NORTH EASTERN DIABETES SOCIETY

DIABETES UPDATE

2025

VOLUME VII

Editor
Dr Mukut Roy

Chief Editor
Dr Mridul Das

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Dr Mukut Roy
mukutdoc@gmail.com

Chief Editor:
Dr Mridul Das

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FOREWORD

It is a great pleasure to present and release the 7th Volume of the Diabetes Update of the North Eastern Diabetes Society (NEDS), during its 30th Annual Conference (NEDSCON 2025) held on 14th to 16th November 2025 at Guwahati, Assam. This edition reflects the dedication, knowledge and teamwork of Editor and all respected members of the NEDS Diabetes Update Editorial Board and also those reputed authors who contributed for advancing diabetes care in our region.

Diabetes management continues to evolve rapidly. Staying informed about new technologies, treatments, and best practices is vital. This publication offers valuable insights to help healthcare professionals enhance care and improve patient outcomes across the North East India.

We acknowledge and sincerely thank the Editor, the whole Editorial Board members and all the contributors for their commitment and meticulous work in bringing out this beautiful book. Your efforts ensure this publication remains a trusted source of knowledge and inspiration.

Let us continue to learn, share and apply these insights to strengthen diabetes care for our communities.

Warm regards,

Dr Rupam Das
Secretary, NEDS

Dr (Prof) Sarojini Dutta Choudhury
President, NEDS

Dr Mridul Das
Chief Editor,
Diabetes Update 2025

PREFACE

“ प्रयोगज्ञानविज्ञानसिद्धिसिद्धाः सुखप्रदाः |
जीविताभिसरास्ते स्युर्वैद्यत्वं तेष्ववस्थितमिति||५३||”

“ Those practitioners who are accomplished in administration of therapies, insight, and knowledge of therapeutics, are endowed with infallible success and can bring happiness to the seeker. ”

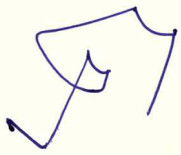
(Charaka Sutra Sthana, Chapter 11: Verse 53)

The Hindu physicians, Charaka and Sushruta, between 400 and 500 BC, were probably the first to recognize the sweetness of diabetic urine and also noted that the diabetes was most prevalent in those who were indolent, overweight and who indulged in sweet and fatty foods. Over the years, the management of diabetes still remains a foremost health challenge and in spite of many efforts, its prevalence is increasing at a distressing rate, especially in our country. North Eastern part of India is not immune to the burden of diabetes and its complications. Along with the recent developments in the classification and etiopathogenesis of diabetes, there have been major advances in the treatment of diabetes. Beyond the gluco-centric view of diabetes, major cardiovascular trials continue to evolve the practice of diabetes and management guidelines are modified accordingly.

North Eastern Diabetes Society (NEDS), has been working hard to keep pace with all those developments in the field of diabetes and publishes Diabetes Updates in regular intervals for the knowledge upliftment of Doctors, Nurses and Paramedics of the North Eastern region and also for the rest of the country. NEDS has already published six (6) updates earlier, last one in 2022. Following this decent philosophy, this time again the Organising Committee of NEDSCON 2025 and Executive Body of NEDS, has decided to bring out this current issue of Diabetes Update and the responsibility was endowed upon me and the Editorial Team. I will remain ever grateful to the Executive Body of NEDS, Organising Committee of NEDSCON 2025 and all other members of NEDS to have confidence on me and our current Editorial Team.

I, under the motivation of Editorial Advisors and Chief Editor, along with the help of Editorial Coordinators and Section Editors, tried my level best to keep the updated scientific developments in this current Diabetes Update 2025. I am grateful to Editorial Advisors, Chief Editor, Editorial Coordinators, Section Editors and all other well-wishers whose reassurance helped me a lot from time to time. I must thank all the contributors for providing manuscripts and sharing their valuable knowledge in their respective chapters. I also express my sincere gratitude to Mr Manabendra Dutta Baruah for compiling and designing the Update and Seven Stars Publications Pvt. Ltd., Guwahati, Assam for the phenomenal effort in printing this Update. It gives me immense pleasure to acknowledge the continuous support of my wife Mrs Susmita Sarkar Roy, sons, mother and my elder sister which remains the significant driving force in completing the task. Finally, on behalf of entire Editorial Board, I do apologize for any unintentional omission or mistake or any printing error in this Current Update in spite of our best efforts. Let's pray to almighty God that NEDS may continue to enrich the field of Diabetes and health of patients with Diabetes.

With best wishes



Dr (Prof) Mukut Roy

Editor, Diabetes Update 2025
30th NEDSCON, Guwahati

Contents

CONTENTS

Contributors

Dr Abhamoni Baro
MD (Medicine), DM (Endocrinology),
Associate Professor, Department of Endocrinology, Gauhati Medical College & Hospital, Guwahati, Assam

Dr Abhijit Sarkar
MD (Medicine), DM Resident (Endocrinology),
Gauhati Medical College & Hospital, Guwahati, Assam

Dr Alokjyoti Malakar
MD (Medicine), DM(Cardiology),
Associate Professor, Department of Cardiology, Jorhat Medical College & Hospital, Jorhat, Assam

Dr Anirban Majumder
MD (Medicine), DM (Endocrinology), FRCP (London), FACE (USA)
Professor, Department of Endocrinology, K P C Medical College, Kolkata, West Bengal

Dr Anupam Dutta
MD (Medicine), Associate Professor, Department of Medicine,
Assam Medical College and Hospital, Dibrugarh, Assam

Dr Arjun Baidya
MD (Medicine), DM (Endocrinology),
Professor, Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, India

Dr Arundhati Das
MD (Medicine),
Post-Doctoral Trainee, Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal

Dr Arundhati Dasgupta
MD (Medicine), DM(Endocrinology), FACE (USA),
Director and Senior Consultant Endocrinologist, Rudraksh Super-speciality Care, Siliguri, West Bengal

Dr Aishwarya R Chandran
DNB (Medicine), Department of Medicine, Nazareth Hospital, Shillong, Meghalaya

Dr Anyam Borpuzari
MBBS, MO - NHM Assam, Assam

Dr Avik Chakraborty
MD (Medicine), FIACM, FICP, FRCP,
Professor, Department of Medicine, Tripura Medical College & Dr BRAM Teaching Hospital, Agartala, Tripura

Dr Ayondyuti Bora
MD (Medicine), MRCP (UK),
Senior Consultant Physician, Tinsukia, Assam

Dr Banshi Saboo
MD(Medicine), PhD.
Dia Care Hormone Clinic, Ahmedabad, Gujrat

Dr Basab Ghosh
MBBS, MDRC,
Senior Diabetologist, Agartala, Tripura

Dr Bhargab Protim Borah
MBBS, Post Graduate Trainee, Department of Medicine, Jorhat Medical College, Jorhat, Assam

Dr Bharat Bhushan Kukreja
MD(Medicine),
Senior Consultant Physician, Marwari Hospital, Guwahati, Assam

Dr Bidita Khandelwal
MD (Medicine),
Professor and Head, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, Gangtok, Sikkim

Dr Bikash Bhattacharjee
MBBS, GDipDC, MDC,
Director and Senior Consultant Diabetologist, Sun Valley Hospital, Guwahati, Assam

Dr Bipul Chandra Kalita
MD (Medicine), FICP
Professor, Department of Medicine, Tinsukia Medical College, Tinsukia, Assam

Dr Bipul Kumar Choudhury
MD (Medicine), DM(Endocrinology)
Senior Consultant Endocrinologist, Guwahati, Assam

Dr Brajendra Lahkar
MD (Medicine), FICP,
Clinical Director, Internal Medicine & Critical Care Medicine, Health City Hospital, Khanapara, Guwahati, Assam

Dr Chanchal Das
MD (Medicine), DCH, DM (Endocrinology)
Senior Consultant Endocrinologist, Probe Diagnostic Centre and Polyclinic,
Sealdah, Kolkata, West Bengal

Dr Chandan Sarmah
MD(Medicine), FICP,
Senior Consultant Physician, Tinsukia, Assam

Dr. Debomallya Bhuyan
MD (Medicine),
Senior Consultant Physician and Head, Department of Medicine, Nazareth Hospital, Shillong, Meghalaya

Dr Devraj Saha
MD (Medicine),
Assistant Professor, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, Gangtok, Sikkim

Dr Dinesh Agarwal
MD (Medicine),
Senior Consultant Physician and Head, Department of Medicine, Marwari Hospital, Guwahati, Assam

Dr Guliver Potsangbam
MD (Medicine), DM (Nephrology), Consultant Nephrologist, Shija Hospitals and Research Institute, Imphal, Manipur

Dr Harshdeep V Nariya
DNB (Medicine), 2nd year Resident
Down Town Hospital, Guwahati, Assam

Dr Hemanga Barman
MBBS, Fellowship in Clinical Diabetology, MGR University, Chennai,
Senior Diabetologist, Sun Valley Hospital, Guwahati, Assam

Dr Iain Charles Pearson Cranston
Lead Diabetes Clinician, Wessex renal and transplant centre, UK, Clinical Research Scientist, Guys, Kings College and St Thomas' Hospitals, Founder and Director, AGP Clinical Academy, Senior Diabetes Physician, Portsmouth, UK

Dr Indira Maisnam
MD (Medicine), DM (Endocrinology), FRCP (Edin), FACE (USA)
Department of Endocrinology, Institute of Post-Graduate Medical Education and Research, Kolkata

Dr Jayanta Kumar Panda
MD (Medicine), FICP, FIMAMS, FRSSDI, Fellow Diabetes India,
FACP (USA), FRCP (London), Professor, Department of Medicine,
SCB Medical College, Cuttack, Odisha

Dr Karuna K Barman
MBBS, Fellowship in Diabetes,
Senior Consultant Diabetologist, Guwahati, Assam

Dr. Ksh. Achouba Singh
MD (Medicine), DM (Endocrinology),
Professor and Head, Department of Endocrinology, JNIMS, Porompat, Imphal, Manipur

Dr Kunjan Saikia
MD (Medicine), DM (Endocrinology), Consultant Endocrinologist,
The Endocrine Clinic, Dibrugarh, Assam

Dr Manoj Kumar Gogoi
MD (Medicine), FICP, Fellow Diabetes India,
Senior Consultant Physician & Diabetologist,
Rontix Hospital, Margherita, Tinsukia, Assam

Dr N K Singh
MD (Medicine), FICP, FACP, F-RSSDI
Director, Department of Diabetology, Diabetes and Heart Research Centre, Dhanbad, Jharkhand

Dr Naruttam Sonowal
MD (Medicine),
Professor, Department of General Medicine, Jorhat Medical College, Jorhat, Assam

Dr Nilakshi Deka
MD (Medicine), DM (Endocrinology)
Consultant Endocrinologist, Apollo Hospital, Guwahati, Assam

Dr Niladri Das
MD (Medicine),
Senior Resident, Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal

Dr Nilanjan Sengupta
MD (Medicine), DM (Endocrinology)
Professor and Head, Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal

Dr Nitin Kapoor
MD (Medicine), DM (Endocrinology),
Post Doc Fellowship (Endo), PhD (University of Melbourne)
Professor, Department of Endocrinology, Diabetes and Metabolism,
Christian Medical College, Vellore, Tamil Nadu

Dr Parvati Nandy
MD (Medicine),
Professor, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, Gangtok, Sikkim

Dr Phibakordor L Nonglait
MD (Medicine), DM (Endocrinology),
Consultant Endocrinologist, Shillong, Meghalaya

Dr Pranab K Biswas
MBBS, Diploma Diabetes Care & Master Diabetes Care (University of New Castle, Australia),
Senior Consultant Diabetologist, Diabetes Care Point, Guwahati, Assam

Dr Pranab Kumar Sahana
MD (Medicine), DM (Endocrinology),
Professor, Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal

Mrs Purabi Dutta
Senior Dietician,
Downtown hospital, Gauhati, Assam

Dr Rajat Deb
MD (Medicine), DM (Endocrinology),
Assistant Professor, Department of Medicine, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh

Dr Rebecca John
MD (Medicine), DM (Endocrinology),
Assistant Professor, Department of Endocrinology, Diabetes and Metabolism,
Christian Medical College, Vellore, Tamil Nadu

Dr Ripun Borpuzari
MD(Medicine), FICP, F.Diabetes India,
Senior Consultant Physician and Diabetologist, Sivasagar, Assam

Dr Ritesh Agarwal
MD (Medicine), DM (Endocrinology)
Senior Consultant Endocrinologist, Bhubaneswar, Odisha

Dr Roohi Nanda
MD (Medicine),
Senior Resident, Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata

Dr Samik Deb
MBBS, DCP, PG Diploma Diabetes Care (Birmingham, UK), PGDCM, Consultant Diabetologist, Bongaigaon, Assam

Dr Samiran Das
MD(Medicine), DM(Endocrinology),
Consultant Endocrinologist, Swasthyam Super Speciality Clinic, Guwahati, Assam

Dr Sanjeeb Kakati
MD (Medicine),
Professor, Department of Medicine,
Principal, Assam Medical College and Hospital,
Senior Consultant Physician, Dibrugarh, Assam

Dr Santosh Adhikari
MD(Medicine), DFID,
Consultant Internist and Diabetologist,
Barman Diabetes Specialities, Guwahati, Assam

Dr Saurav Das
MD(Medicine), DM(Endocrinology),
Consultant Endocrinologist, Marwari Hospital, Guwahati, Assam

Padma Shri (Dr) Shashank R. Joshi
MD(Medicine), DM(Endocrinology),
FRCP (Glasgow & Edinburgh), FACP (USA), FACE (USA), Senior Consultant Endocrinologist, Lilavati Hospital and Research Centre, Mumbai, Maharashtra

Dr Shirshendu Mondal
MD (Medicine), Post-Doctoral Trainee,
Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal

Dr Soumik Goswami
MD (Medicine), DM (Endocrinology)
Assistant Professor, Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal

Dr Subhajyoti Ghosh
MD, PhD (Diabetes),
Apollo Clinic, Graham Bazar, Dibrugarh, Assam

Dr Suranjit Barua
MD(Medicine), FICP
Senior Consultant, Department of Medicine, Down Town Hospital, Guwahati, Assam

Dr Swapnav Borthakur
MD (Medicine),
Consultant, Department of Medicine, Down Town Hospital, Guwahati, Assam

Dr Uma Kaimal Saikia
MD (Medicine), DM (Endocrinology),
Professor, Department of Endocrinology, Gauhati Medical College, Guwahati, Assam

Dr Uttam Kumar Nath
MD (Medicine),
Associate Professor, Department of Medicine, Jorhat Medical College, Jorhat, Assam

Dr Vanlalhruaii
MD (Medicine), Post Doc Fellow in diabetology (CMC Vellore),
Associate Professor & Head, Department of Medicine, Zoram Medical College & Hospital, Mizoram

Section 01

Section Editor : **Noni Gopal Singha**

Analysis and Classification of Diabetes Mellitus

Chapter 01

Approach to Newer Classification of Diabetes

Shashank R. Joshi

INTRODUCTION

Diabetes mellitus is a group of chronic metabolic disorders characterized by elevated blood glucose levels resulting from total or partial insulin deficiency, insulin resistance, or a combination of both. For a long time, the simple classification of diabetes into Type 1 and Type 2 has been used as a workable basis. However, that binary separation does not correspond anymore to the biological and phenotypic variations. Epidemiological studies, immunology and genetics advances, and data, driven analytics all point to the fact that diabetes should be considered as a range of overlapping endotypes with different aetiologies, progression, complications, and responses to therapy. Various phenotypes of diabetes can be found in India and other South Asian regions, from insulin, deficient lean adults to severely insulin, resistant individuals with fatty liver, as well as the condition of undernourished adolescents with low beta cell reserve. Hence, a classification based on the disease mechanism and biomarkers along with age, body weight, or treatment dependence would be more insightful for the decision, making process.

CLASSICAL CLASSIFICATION AND ITS LIMITATIONS

The World Health Organization (WHO) and the American Diabetes Association (ADA) have traditionally grouped diabetes into four categories that remain the operational standard in many guidelines.

Category	Underlying Mechanism	Typical Clinical Features	Key Remarks
Type 1 Diabetes Mellitus	Autoimmune destruction of pancreatic beta cells causing absolute insulin deficiency	Early onset, lean habitus, ketosis-prone	Requires lifelong insulin therapy
Type 2 Diabetes Mellitus	Insulin resistance with relative beta cell failure	Middle-aged, overweight, gradual onset	Most common worldwide
Gestational Diabetes Mellitus	Insulin resistance due to pregnancy-related hormonal changes	Hyperglycaemia first detected in pregnancy	Risk of future Type 2 diabetes
Other Specific Types	Genetic defects, pancreatic disease, endocrinopathies, drugs, infections	Variable	Includes MODY, pancreatitis, steroid-induced diabetes

Table 1: Conventional WHO and ADA Classification of Diabetes Mellitus

Many adults diagnosed as Type 2 are antibody-positive or have low C-peptide. Others present with ketosis and later maintain glycaemic control without insulin. The classical categories offer limited prognostic precision and do not guide targeted therapy for intermediate or atypical forms such as latent autoimmune diabetes in adults, ketosis-prone diabetes, or malnutrition-related diabetes.

RATIONALE FOR A NEWER CLASSIFICATION

The decision to move towards reclassification of a disease is supported mainly by the following pillars:

monogenic and molecularly distinct forms. Data, driven modelling reveals reproducible clusters that correspond to the pathophysiology. Such a mechanism, centric taxonomy that combines clinical variables with biomarkers not only provides a more accurate map of disease biology but also a feasible way to personalised therapy.

CLUSTER BASED CLASSIFICATION

Cluster, based classification uses six variables readily available in adults with new, onset diabetes. The variables were age at diagnosis, body mass index, HbA1c, GAD antibody status, and fasting,

Cluster	Abbreviation	Dominant Mechanism	Clinical Profile	Predominant Complications
Severe Autoimmune Diabetes	SAID	Autoimmune beta cell destruction	Lean, younger, antibody-positive, low C-peptide	Ketoacidosis, early retinopathy
Severe Insulin-Deficient Diabetes	SIDD	Non-autoimmune beta cell failure	Lean or normal BMI, very high HbA1c, low C-peptide	Retinopathy, rapid progression
Severe Insulin-Resistant Diabetes	SIRD	Marked insulin resistance	Obese, high HOMA-IR, fatty liver common	Nephropathy, cardiovascular disease
Mild Obesity-Related Diabetes	MOD	Obesity with modest insulin resistance	Obese, younger adults, slower rise in HbA1c	Lower complication burden
Mild Age-Related Diabetes	MARD	Age-linked decline in beta cell function	Older onset, mild dysglycaemia	Slowest progression

Table 2: Five Pathophysiologic Clusters of Diabetes (Ahlqvist et al.)

Hyperglycaemia in the case of diabetes arises from multiple pathways with different proportions of insulin resistance and insulin secretion. For example, South Asians often develop diabetes at a lower body mass index and at a younger age, usually with a combination of insulin deficiency and resistance. Genomics and metabolomics now can identify

derived indices of insulin resistance and beta, cell function.

The clusters account for the different therapeutic responses that occur in people who have been categorized as those with Type 2 diabetes. Those in SAID and SIDD receive a positive effect from the

early use of insulin or the administration of agents that can help in the beta cell function such as GLP, 1 receptor agonists. In contrast, patients in SIRD need the help of insulin sensitisation done by metformin, thiazolidinediones, and in most cases GLP, 1 receptor agonists, accompanied by the firm reduction of cardiovascular risk. Lifestyle changes and oral therapy usually show good results in MOD and MARD. The biology of the clusters is also associated with the complications that accompany them. For example, renal disease is the most common in SIRD, while retinopathy at an early stage is the peculiar feature of SIDD. MARD has a slow progression. The cluster paradigm thus facilitates the implementation of precision screening schedules, pharmacotherapy that is tailored, and long, term counselling that is realistic in nature.

THE INDIAN AND SOUTH ASIAN CONTEXT

India is a major contributor to the world's diabetes burden and has unique phenotypes. The onset of diabetes is sometimes 10 years earlier than in the Western populations and at a lower BMI. The common features are visceral adiposity with the relative loss of muscle mass and the history of undernutrition in the early years followed by overnutrition in the later years. These factors influence the dual burden of insulin insufficiency and insulin resistance.

Research work in India has shown that most of the adult population is divided into SIDD and SIRD, with fewer people in MOD and MARD. Diabetes caused by malnutrition is still a significant problem in low, income areas. These are the facts that point to the necessity of the population, specific setting of cluster threshold levels and the policies that aim to provide solutions for both ends of the nutrition spectrum.

SPECIFIC AND NEWLY RECOGNISED FORMS

Monogenic diabetes

Monogenic diabetes is a small group of diabetes (1, 2%) caused by single, gene variants affecting beta cell development or insulin secretion. Mutations in HNF1A, HNF4A, and GCK are the most prevalent. Features indicating monogenic diabetes may include disease onset before the age of 25, strong autosomal dominant family history, non, obese habitus, preserved C, peptide, and negative autoantibodies. A genetic test confirms the diagnosis. The treatment varies depending on the gene. Patients with HNF1A and HNF4A mutations usually take sulfonylurea at a low dose and achieve good glycaemic control. In GCK mutations, mild fasting hyperglycaemia is

Parameter	Indian Population	Western Population
Mean BMI at diagnosis	23 to 25 kg m^{-2}	28 to 30 kg m^{-2}
Dominant mechanism	Combined insulin deficiency and resistance	Predominantly resistance
Common subtypes	SIDD, SIRD, Type 5 diabetes	MOD, MARD
Typical age of onset	30s to 40s	50s to 60s
Key modifiers	Early undernutrition, visceral adiposity, sarcopenia	Obesity, sedentary behaviour

Table 3: Comparison Between Indian and Western Diabetes Phenotypes

stable and pharmacotherapy is often unnecessary. Proper diagnosis prevents the use of insulin unnecessarily for life and enables relatives screening.

Latent autoimmune diabetes in adults

LADA develops after the age of 30, with a gradual autoimmune destruction of beta cells. Patients are typically thin and respond well to an oral agent in the initial phase, however, within a few years, insulin therapy becomes necessary. The presence of GAD or IA, 2 antibodies and low or decreasing C, peptide levels are diagnostic features of LADA. To maintain the residual beta cell function, it is recommended to start insulin therapy early.

Ketosis prone diabetes

Ketosis, prone diabetes or Flatbush diabetes is a condition that mainly affects male population of African or South Asian origin. The common feature at presentation is diabetic ketoacidosis. The majority of patients after recovery show beta cell function that is still preserved and hence, they are able to maintain glycaemic control without insulin. Most of them are antibody, negative. Aβ system segregates patients by autoimmunity and beta cell function and is useful for long, term prognosis.

Malnutrition related or Type 5 diabetes

Insufficient nutrition during childhood and adolescence can lead to the impaired pancreatic development and consequently reduced beta cell capacity for a lifetime. The International Diabetes Federation has given this condition the name of Type 5 diabetes. The individuals are usually underfed and show signs of stunting. They manifest severe hyperglycaemia without ketosis, have low C, peptide levels, and are negative for antibodies. Treatment involves combining low, dose basal insulin with nutritional rehabilitation. Identifying this form is significant to public health planning that is fair and targeted toward the less privileged.

Secondary diabetes

Secondary diabetes is the result of specific causes. Chronic pancreatitis, cystic fibrosis, pancreatic malignancy, endocrinopathies e.g. Cushing syndrome or acromegaly, medicines e.g. glucocorticoids and antipsychotics, and post, transplant states are some of these causes. Besides glycaemic control, the treatment should focus on the underlying disease.

BIOMARKERS AND INVESTIGATIVE APPROACH

Laboratory and clinical indicators assist in assigning subtype, even when resources are limited.

In many clinics, a practical combination of age at

Parameter	Purpose	Interpretation
GAD, IA-2, ZnT8 antibodies	Detect autoimmune aetiology	Positive in Type 1 diabetes or LADA
C-peptide, fasting or stimulated	Measure endogenous insulin secretion	Low in SIDD and Type 5, high in SIRD and MOD
HOMA-IR and HOMA-B	Quantify insulin resistance and beta cell function	Guides cluster assignment
Genetic testing panels	Confirm monogenic diabetes	Positive in MODY subtypes
Liver enzymes and hepatic fat indices	Surrogates of hepatic insulin resistance	Elevated in SIRD and NAFLD
Anthropometry and nutrition indices	Assess adiposity and undernutrition	Favour SIRD or Type 5 respectively

Table 4: Key Biomarkers and Their Role in Classification

onset, BMI, family history, C-peptide, and a single autoantibody is sufficient to distinguish the main endotypes with useful accuracy. Repeat testing over time is valuable because phenotype may evolve.

PRACTICAL ALGORITHM FOR PINPOINTING SUBTYPES

A structured bedside approach reduces misclassification and guides therapy.

One's therapy ought to be linked to their mechanism. In deficiency states, insulin is required earlier, whereas in resistance states, insulin sensitisation along with comprehensive cardiovascular risk management is advisable. Mixed states should be managed with combination strategies. Nutritional support is a necessary part of Type 5 diabetes.

Step	Key Evaluation	Interpretation Guide
1	History and examination	Document age at diagnosis, BMI, waist–hip ratio, family history, nutrition, ketosis history
2	Baseline labs	HbA1c, fasting glucose, lipid profile, liver enzymes
3	Beta cell and immunity	Fasting or stimulated C-peptide, GAD and IA-2 antibodies where possible
4	Insulin resistance	Calculate HOMA-IR if fasting insulin is available
5	Provisional subtype	Use Table 6 below to map findings to likely endotype
6	Re-evaluate	Reassess C-peptide and control yearly, adjust subtype if course diverges

Table 5: Stepwise Clinical Approach to Subtype Identification

Findings	Probable Subtype	Treatment Focus
Antibody positive and low C-peptide	Type 1 diabetes or LADA	Early and sustained insulin therapy
Antibody negative and low C-peptide	SIDD or Type 5 diabetes	Insulin or GLP-1 receptor agonist plus nutrition if Type 5
Antibody negative with high C-peptide and obesity or NAFLD	SIRD or MOD	Metformin, thiazolidinedione, GLP-1 receptor agonist, intensive cardiometabolic care
Early onset with multigenerational family history and preserved C-peptide	Monogenic diabetes	Genetic confirmation, sulfonylurea in HNF1A or HNF4A
DKA at presentation followed by remission of insulin need	Ketosis-prone diabetes	Short-term insulin then oral agents with relapse surveillance
Older onset with mild dysglycaemia and slow progression	MARD	Lifestyle therapy and oral agents, gradual titration

Table 6: Clinical Clues and Corresponding Diabetes Subtypes

CASE ILLUSTRATIONS

28, year, old thin male came to the clinic complaining of polyuria and weight loss. HbA1c was 10.8 percent. The tests for antibodies were negative, and fasting C peptide was low. He is a perfect example of SIDD. After starting basal, bolus insulin, the treatment was later simplified to basal insulin with an add, on GLP 1 receptor agonist. The main focus was on retinopathy screening.

45, year, old woman with a BMI of 33 kg/m² and fatty liver confirmed by ultrasound had an HbA1c of 8.4 percent and very high fasting insulin. She is a case of SIRD. The patient was given metformin and pioglitazone; a GLP1 receptor agonist was also prescribed for weight and liver fat reduction. Blood pressure and lipids were managed according to the guidelines. Urine albumin is checked every six months.

21, year, old non, obese female with stable fasting glucose close to 120 mg/dl, good C peptide, negative antibodies, and a strong family history of diabetes at a young age was referred for genetic testing that revealed an HNF1A variant. She was taken off metformin and given low, dose gliclazide which resulted in good glycaemic control. Relatives are invited to undergo cascade testing and are counselled accordingly. These vignettes illustrate how mechanism, based categorization affects changes in therapy, surveillance, and counselling.

PUBLIC HEALTH IMPLICATIONS

India is challenged by two simultaneous problems. Insulin, resistant states associated with obesity, physical inactivity, and dietary patterns are mainly responsible for urban and peri, urban regions. However, malnutrition, related diabetes can still be found in rural and impoverished areas. Incorrect classification of the disease results in the wrong selection of drugs, the prevention of complications going unrecognized, and resources being used inefficiently. National programs that incorporate cluster, based rules can help in the identification and consequent prioritization of subgroups who are at high risk. For example, the group SIRD requires thorough renal surveillance and cardioprotective therapy, while SIDD deserves early retinal screening and education on insulin use. Nutrition, related diabetes identification necessitates community nutrition and social support integration. By capturing C peptide, antibody, BMI, and simple clinical variables, registries can help regional planning become more efficient as well as equitable.

DIGITAL HEALTH APPLICATIONS

Electronic medical records may facilitate subtype identification without imposing heavy demands on clinicians. The software implementation can calculate HOMA indices from fasting glucose and insulin, keep records of weight and waist changes, and issue antibody or C peptide testing notifications when the profile is unusual. Endotypes that are likely to be present and evidence, based therapy initiation can be inferred by decision support. Indian machine learning models built on longitudinal sets can predict progression, insulin requirement, and complication risk, thus modifying patient subtyping in real, time as further data come in. If the right management is in place, this equipment can bring precision diabetology to primary healthcare level.

FUTURE DIRECTIONS

Diabetes classification is progressively leaning towards molecular genotyping, epigenetic insights, and dynamic, data, rich profiling. Proteomic and metabolomic signatures that separate insulin resistance from secretory failure are being uncovered by multi, omics studies. The developmental origins of health and disease framework are connecting intrauterine and early childhood undernutrition with adult beta, cell vulnerability. Cluster thresholds and risk algorithms need to be adjusted to fit the Asian populations who have lower BMI and different body compositions. Eventually, static labels will be replaced by adaptive profiles that take into account each person's changing path, surroundings, and response to treatment.

PRACTICAL SUMMARY FOR CLINICIANS

1. Record age at diagnosis, BMI, waist–hip ratio, family history, and nutritional status before assigning a label.
2. Obtain C-peptide and at least one autoantibody where feasible.
3. Use simple logic: low C-peptide indicates deficiency, high C-peptide with obesity indicates resistance, antibodies indicate autoimmunity.
4. Consider monogenic diabetes in young non-obese patients with multigenerational history.
5. Reassess subtype as disease evolves or therapy response diverges from expectation.
6. Match therapy to mechanism and align complication screening with the endotype's risk pattern.

CONCLUSION

Diabetes mellitus is not a single disease. It is a family of related disorders unified by hyperglycaemia but diverse in origin and course. A modern classification grounded in mechanism illuminates that diversity and translates into better clinical care. The cluster-based framework and recognition of monogenic, ketosis-prone, and malnutrition-related forms allow purposeful treatment, smarter surveillance, and clearer communication with patients. In India, where phenotypic heterogeneity is wide, this approach is essential. The convergence of clinical expertise, biomarker testing, and digital decision support can move everyday practice toward precision diabetology and improved outcomes.

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Chapter 02

Defining and Understanding Gestational Diabetes Mellitus

Vanlalhruaii

INTRODUCTION

In the words of my wise teachers, Diabetes begets Diabetes. To break this chain of vicious cycle, the general practitioner must be aware of the principles of gestational diabetes mellitus (GDM) . We have to ensure that management of GDM does not end with delivery of the baby but requires a lifelong management. Glucose intolerance developing during the second or third trimester of pregnancy is classified as gestational diabetes mellitus (GDM). Insulin resistance is related to the metabolic and hormonal changes of pregnancy, during which the increased insulin demands and insulin resistance may lead to IGT or diabetes. The American Diabetes Association (ADA) recommends that diabetes diagnosed within the first trimester be classified as pre-existing pregestational diabetes rather than GDM. Most women with GDM revert to normal glucose tolerance postpartum but have a substantial risk (35–60%) of developing DM in the next 10–20 years, a lifetime maternal risk for diabetes estimated at 50–60%.

RISKS ASSOCIATED WITH GDM:

Potential risks associated with gestational diabetes mellitus

	Comment
Short-term	
Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)	• Preeclampsia can be life-threatening • These disorders often lead to medically-indicated preterm birth
Large for gestational age newborn or macrosomia	• May result in maternal or neonatal birth trauma (eg, from shoulder dystocia) • Macrosomia is an indication for planned cesarean birth
Polyhydramnios	• Usually mild
Operative delivery (cesarean birth, forceps- or vacuum-assisted vaginal birth)	
Fetal/neonatal cardiomyopathy	• Usually asymptomatic, but 5 to 10% have respiratory distress or signs of poor cardiac output or heart failure • Most often in the setting of suboptimal glucose levels
Neonatal respiratory problems	• Usually mild. • Most often in the setting of suboptimal glucose control. Fetal/neonatal hyperinsulinemia appears to delay surfactant synthesis.
Neonatal metabolic problems (hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia and hyperviscosity syndrome)	• Most often in the setting of suboptimal glucose control • Hypoglycemia and hyperbilirubinemia are the most common metabolic problems
Longterm	
Maternal	
• Diabetes mellitus (primarily type 2)	• The lifetime maternal risk for diabetes is estimated to be 50 to 60%
• Cardiovascular disease	• Individuals with GDM are at higher risk of developing cardiovascular disease and developing it at a younger age than those with no history of GDM
Offspring	
• Diabetes mellitus • Obesity • Hypertension • Metabolic syndrome • Possibly adverse neurodevelopment	

The risks of these outcomes increase as maternal fasting plasma glucose levels increase above 75 mg/dL (4.2 mmol/L) and as the one- and two-hour oral glucose tolerance test values increase from the lowest septile to the highest. This is a continuous effect; there is no clear threshold that defines patients at increased risk of adverse obstetric outcome.

The small increase in congenital anomalies observed in some population-based studies of GDM is likely related to undiagnosed preexisting type 2 diabetes mellitus or maternal obesity.

GDM: gestational diabetes mellitus.

PREVALENCE OF GDM IN INDIA

A systematic review and meta-analysis published in 2024 estimates the prevalence of GDM to be 13% all over India. In East and North-eastern Region, the pooled prevalence was found to be 11.5%**.** In this review, DIPSI was the most common diagnostic criteria used, followed by International Association of Diabetes and Pregnancy Study Groups (IADPSG) and World Health Organization (WHO) 1999.

METHODS OF DIAGNOSIS

ADA 2025

GDM diagnosis can be accomplished with either of two strategies:

- 1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
- 2. The "two-step" approach with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive based on Carpenter-Coustan's criteria.

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when an individual is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

Fasting: 92 mg/dL (5.1 mmol/L)

1 hour: 180 mg/dL (10.0 mmol/L)

2 hours: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (non-fasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL, proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the individual is fasting.

The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria):

Fasting: 95 mg/dL (5.3 mmol/L)

1 hour: 180 mg/dL (10.0 mmol/L)

2 hours: 155 mg/dL (8.6 mmol/L)

3 hours: 140 mg/dL (7.8 mmol/L)

DIPS

Diabetes in Pregnancy Study Group India (DIPSI) developed a one-step process to detect GDM, irrespective of their last meal. After administering 75 g of anhydrous glucose dissolved in 250–300 mL of water, the plasma glucose level in pregnant women will be measured 2 hours after consumption. Plasma glucose levels of ≥140 mg/dL are taken as GDM. DIPSI recommends universal screening of all pregnant women at their first ANC. All antenatal women who have been tested in first trimester and were screened negative will undergo second testing at 24-28 weeks. Antenatal women coming after 28 weeks for first test will undergo only one test.

A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method. The IADPSG criteria (one-step strategy) have been adopted internationally as the preferred approach. Data that compare population-wide outcome with one-step versus two-step approaches have been inconsistent to date. Longer-term outcome studies are currently underway.

With different hospitals and institutions adopting their own methods and criteria for screening, it is impertinent to have a uniform guideline and method for screening to enforce more robust diagnosis of cases. One- step method definitely has an advantage over the two- step method when it comes to practical

issues and has been proven by several studies across the globe.

GLYCEMIC TARGETS

Fasting, pre-prandial, and post- prandial blood glucose monitoring are recommended in individuals with diabetes in pregnancy to achieve optimal glucose levels.

Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C goal in pregnancy is <6% if this can be achieved without significant hypoglycaemia, but the goal may be relaxed to <7% to prevent hypoglycemia. Continuous glucose monitoring (CGM) can help to achieve glycemic goals and A1C goal in any type of diabetes in pregnancy.

Glucose measurement	Blood glucose goal		
	Type 1 or type 2 diabetes	GDM treated with insulin	GDM not
Fasting glucose	70–95 mg/dL (	70–95 mg/dL	<95 mg/dL
1-h postprandial glucose	110–140 mg/dL	110–140 mg/dL	<140 mg/dL
2-h postprandial glucose	100–120 mg/dL	100–120 mg/dL	<120 mg/dL

INSULIN PHYSIOLOGY

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than those in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental factors. Early pregnancy may be a time of enhanced insulin sensitivity and lower glucose levels and is followed by progressive insulin resistance in the second and third trimesters. Insulin resistance drops rapidly with the delivery of the placenta. In people with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in people with diabetes, hyperglycaemia occurs if treatment is not adjusted appropriately.

GLUCOSE MONITORING

Reflecting this physiology, fasting and post- prandial blood glucose monitoring is recommended to achieve glycaemic goals in pregnant people with diabetes. Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy. Therefore, it should not be used as the mainstay of monitoring during pregnancy. In the second and third trimesters, A1C <6% has the lowest risk of complications. Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycaemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

MANAGEMENT

According to DIPSI Guidelines 2023:

- Medical nutrition therapy and physical exercise for 2 weeks
- If PPBS is above target, then start pharmacological therapy
- Metformin or insulin are the accepted medical management of GDM
- Metformin is to be considered after 20 weeks of pregnancy
- Insulin may be started any time during the pregnancy
- Insulin may be started before 20 weeks of pregnancy or after 20 weeks of pregnancy as an addition to Metformin (DIPSI)

Insulin is the drug of choice in the management of GDM. DIPSI, RSSDI, NICE, ACOG, IDF have all recommended the use of both human insulin and insulin analogue in pregnancy with diabetes. The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. The insulin requirement rises as the pregnancy progresses. Most of the patients will require basal bolus insulin regimen rather than premixed insulin. Maintaining euglycemia is crucial to the wellbeing of the foetus. For this reason, close and structured monitoring must be advised and the patient must be either assisted or advised on proper titration of her insulin dose to achieve glycaemic target without risking hypoglycaemia. The insulin requirement levels off toward the end of the third trimester.

Metformin has a lower risk of neonatal hypoglycaemia and less maternal weight gain than insulin in systematic reviews and RCTs for GDM treatment. But there is a high chance of treatment monotherapy failure, up to 14–46%. A retrospective analysis of 540 women from South India with diabetes in pregnancy published in 2018 concluded that the initiation of metformin within the first trimester of pregnancy has no significant adverse maternal or foetal outcomes, although they advised caution regarding preterm births. Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Compared with insulin or metformin, glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia and an increased neonatal abdominal circumference.

In spite of all these advised cautions, being in a resource limited country, we still have many patients facing financial issues. This is often the peril of the pregnant, daughter- in – law who is financially dependent on her spouse. For these group of patients, the safe and effective use of insulin with the added challenges of peripartum care may be unfathomable. In such conditions, oral agents may be the first and only alternative albeit after discussion of known risks and the need for wider data in offspring; all these keeping in mind the absolute contraindications.

POST PARTUM CARE

Breastfeeding is recommended for individuals with GDM and has been shown to reduce the risk for type 2 diabetes later in life. We must screen GDM patients at 4–12 weeks postpartum using the 75-g oral glucose tolerance test and nonpregnancy diagnostic criteria. If both the fasting plasma glucose and 2-h plasma glucose are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists. Individuals with a history of GDM should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years.

Together we must strive to nip Diabetes in the bud.

May NEDS prosper.

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Section 02

Section Editor : **Debomallya Bhuyan**

Epidemiology of Diabetes Mellitus

Chapter 03

Methodologic Issues in the epidemiology of type 2 diabetes in Indian Sub context

Chanchal Das

INTRODUCTION

The age distribution of sample populations is crucial in studying type 2 diabetes mellitus (T2DM), whose prevalence rises with age; study populations must be age - stratified and any comparisons age adjusted, either within the data set, or standardized against a reference population. Finally, ascertainment methods are important − for example, whether subjects undergo an oral glucose tolerance test (OGTT), with or without preliminary blood glucose screening. India is second largest populous country having the extremely high prevalence of T2DM of the globe with more than 101 million people living with diabetes. As per latest Indian Council of Medical Research-India Diabetes Study report (ICMR–INDIAB) prevalence of diabetes and prediabetes are 11.4% and 15.3% respectively in adults of aged more than 20 years. Studies conducted in different regions of the world have highlighted an increase in the prevalence of T2DM. While few would argue that this translates into increasing burden associated with diabetes, it is important to recognize the factors that have contributed to this increased prevalence.

METHODOLOGIC ISSUES IN THE EPIDEMIOLOGY

Several factors directly affect the prevalence of diabetes, and may partly account for the

increasing prevalence:

1) Changes in the ratio of diagnosed: undiagnosed cases of diabetes,

2) Population demographic changes with an aging population,

3) Earlier age at onset of diabetes,

4) Longer survival in patients with diabetes than before,

5) Increasing incidence of diabetes.

The different factors may have different contributions depending on the population being studied, although most if not all are of some importance in most populations.

The epidemiology and prevalence of diabetes is partly determined by the diagnostic criteria used to diagnose diabetes. The diagnostic criteria have been modified on a number of occasions. These modifications definitely have some impact on the study. With the American Diabetes Association (ADA) and World Health Organization (WHO) classification of 1999, the threshold of fasting glucose as diagnostic criteria of diabetes was lowered from 140 mg/dl to 126 mg/dl. These changes increased the number of diabetes cases because a greater number of subjects fulfilled the criteria for diagnosis of T2DM. A fasting glucose between 6.0 and < 7 mmol/L (108 mg/dl and 126 mg/dl) was previously considered to be pre - diabetic and the term impaired fasting glucose (IFG) was used. Subsequent lowering of the “normal” fasting glucose level to 5.6 mmol/L (100 mg/dl) further increases the number of patients with “pre - diabetes. It is important to know which method has been chosen in an epidemiologic survey for the diagnosis of

diabetes-elevated fasting glucose or post - load values during an oral glucose tolerance test (OGTT). Diagnosis made by post glucose load during an 2 h OGTT clearly picked up more subjects as diabetes than elevated fasting glucose value. Lower threshold for diagnosing IFG in the recommendation by the ADA (100 mg/dl) will result in a larger number of subjects diagnosed to have intermediate hyperglycemia than the WHO recommendation (110 mg/dl). Increased diagnostic activity through use of the OGTT will lead to an increased ratio of diagnosed: undiagnosed diabetes, and may impact on the prevalence rate reported in epidemiology studies.

The older serial epidemiological surveys show that there is an increasing trend of prevalence of diabetes in India post 1970s. Recent studies also highlighted that younger population are affected more and more. But most of the epidemiological studies published are from the southern part of the country. One such study Chennai Urban Rural Epidemiology Study (CURES - 17) is showing high prevalence of diabetes of 14.3% with 18.6% in the city of Chennai. Here the study population may not be representative of the whole country and therefore require further study recruiting people from all zones of India. The National Urban Diabetes Survey, carried out in six cities in 2001, found prevalence rates of 12% for diabetes with a slightly higher rate in male and 14% for impaired glucose tolerance (IGT). Subjects under 40 years of age had a prevalence of 5% for diabetes and 13% IGT. In this study the population from only six cities were recruited. There was no recruitment of subjects from rural areas. However, from this study it was evident that diabetes was positively correlated with increasing age, BMI, increased waist hip ratio and a positive family history of diabetes. It was also positively correlated with higher monthly family income and physical inactivity. Several studies showed the difference of prevalence of diabetes between urban and rural areas. Most study showed higher prevalence of diabetes in urban areas compared to rural areas. But recent study revealed that this urban and rural gap is being reduced day by day. A study from Chennai noted a progressive increase in the prevalence rate with increasing urbanization; 2.4% in rural areas, 5.9% in semi urban areas and up to 11.6% in urban areas. Another study which was conducted in both urban and rural areas showed the prevalence of diabetes in the urban area (5.9%) is slightly higher than the rural area (2.7%).

However, most of the epidemiological studies done earlier had been either from metropolitan cities or second-tier cities, with limited data from rural India. There was no national study which comprehensively covered the whole country. This led to the Indian Council of Medical Research–India Diabetes Study (ICMR–INDIAB) being taken up in 2008. ICMR–INDIAB study is a cross-sectional, community-based survey of adults of both sexes aged >20 years representative of every state in the country including urban and rural areas. Mainly driven by the increasing obesity rates incidence of diabetes is rapidly increasing in the South East Asian region including India. The National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) was launched in 2010 in 100 districts across 21 states with an objective to prevent and control major non-communicable diseases is a very good programme from which lots of data are expected regarding diabetes and other non-communicable diseases. The programme was scaled up in a phased manner and now covers all the districts across the country. The government has recently revamped its earlier National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) to the National Programme for Prevention and Control of Non-Communicable Diseases (NPNCD).

In a comprehensive report on the global prevalence of diabetes, it was noted that the most important demographic change to diabetes prevalence across the world was the increase in proportion of people over 65 years of age. Another major factor that has impacted on the prevalence of diabetes is the increasing age-specific prevalence of diabetes, especially in the younger age groups. This suggests

an earlier age of onset of diabetes, which may be of particular importance in low- and middle-income countries. It is also worthwhile noting the tendency for the prevalence rates of IGT to decline as that of diabetes rises, perhaps suggesting that areas with a high ratio of IGT: diabetes are at an earlier stage of the diabetes epidemic and thus may be a particular target for preventative strategies. Changes and variations in the ratio of IGT: diabetes prevalence – the so - called "epidemicity index," may provide a useful marker for the scale of the epidemic in that particular region. According to the latest ICMR report, the prevalence of T2DM in urban area is high but rural areas are rapidly catching up especially for prediabetes. While the diabetes: prediabetes ratios indicate that some of the more economically progressive states have started showing plateauing of diabetes, the prevalence in most states in the country is still on the rise. There are huge interstate and regional differences in prevalence of NCDs like population prevalence of diabetes ranged from 4.8% in Uttar Pradesh to 26.4% in Goa.

CONCLUSION

Before interpreting the results of epidemiological studies in T2DM in India, we should understand the type of epidemiologic methods used in the study. To have a robust epidemiological study it must not have any recruitment bias. The sample size should be large enough to get accurate data. The age distribution of the sample population for the study of T2DM is also important because prevalence of diabetes rises with increasing age. So, the study population must be age standardised and stratified. These are very much important in a country like India where there exists true diversity in various ways like religion, language, weather and life styles including feeding habits although methodologic differences still hamper comparisons between different studies.

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Chapter 04

Environmental risk factors for type 1 diabetes mellitus: Epidemiological Perspective

Phibakordor L Nonglait

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a condition characterised by absolute insulin deficiency and insulin dependence which represents 5-10% of all DM cases. Recent trends have shown an increase in the incidence and prevalence of T1DM worldwide. It is widely recognised that this increase in the incidence of T1DM cannot be explained on the basis of genetics alone but other factors such as environmental influence, microbiome and epigenetics interact in the pathogenesis of the disease. Epidemiological studies have identified various environmental exposures that can interact with genetics and lead to the development of T1DM. In this review we will briefly discuss the environmental determinants on the pathogenesis of T1DM.

ROLE OF VIRUSES

Viruses have been linked with the development and acceleration of T1DM, most notably enteroviruses especially when occurring in early childhood. In addition to enteroviruses, such as Coxsackievirus B, other viruses belonging to different families such as Reoviridae (Rotavirus), Togaviridae (Rubella virus), Paramyxoviridae (Mumps virus), Herpesviridae (Cytomegalovirus and Epstein Barr virus), and the Coronaviridae family (SARS-CoV-2), have been identified as potential environmental factors associated with the risk of developing T1DM. The Environmental Determinants of Diabetes in the Young (TEDDY) identified enterovirus B as the only virus in the human virome with a significant association with islet autoimmunity. These results were based on metagenomic sequencing of monthly stool samples paired with healthy controls collected from newborns until the detection of islet autoimmunity or T1DM. It was also found that children with prolonged excretion of enterovirus B were more likely to develop T1DM. The proposed mechanisms for the etiopathogenesis of viruses in T1DM are

i. Direct infection of the β-cells, as evidenced by the enterovirus proteins detected in the pancreas.

ii. Triggering autoimmunity by inducing autoantibodies against pancreatic β-cells via molecular mimicry.

The recent COVID-19 epidemic has also been linked with an increased incidence of T1DM. The hypothesis proposed are the expression of ACE2 receptors in pancreatic β-cells as well COVID-19 as an exacerbating factor of preclinical type 1 diabetes, highlighting the role of new viruses in the pathogenesis of T1DM and potential for further research.

ROLE OF MICROBIOTA

The relationship between gut microbiota and diabetes is an evolving and complex area even among individuals with T1DM and T2DM. Advances in metabolomics and proteomics have shed light into

the complex relationship between the intestinal microbiota and T1DM and have found.

i. Reduction of the diversity of gut microbiota
ii. Alteration in the Firmicutes/Bacteroides ratio
iii. Decreased number of probiotic bacteria such as lactobacillus

The proposed environmental factors contributing to an altered gut microbiome are caesarean delivery, use of broad-spectrum antibiotics in first 2 years of life, timing of exposure to gluten and exposure to cow's milk. This increases the susceptibility to invasion by pathogenic organisms and an altered inflammatory pathway and ultimately susceptibility to T1DM. Additionally, the composition of the gut microbiome has been shown to alter the metabolism of carbohydrates, fatty acids, and amino acids which predisposes to metabolic disorders including diabetes.

ROLE OF DIET AND VITAMIN D

Diet has an influence on T1DM at different stages of life. Some of these factors may act as a trigger for autoimmunity, while others act as an accelerator for progression from asymptomatic Stage 1 to the symptomatic Stage 3 T1DM.

i. Breastfeeding has been shown to have a protective effect against T1DM in retrospective but not prospective studies including the recent data on TEDDY study. However, children who were still breastfed at the time of introduction to cereals had a reduced risk of islet autoimmunity, and onset of diabetes suggesting a protective role in T1DM.

ii. The timing of introduction of gluten has an effect on antibody expression with a protective effect of early introduction at 4 months as compared to 9 months. In addition, higher total energy intake is associated with higher BMI and increased weight z-scores at 12 months which leads to higher risk of the development of islet autoimmunity.

iii. Role of supplements: Early probiotic exposure among genetically susceptible individuals has a protective role in T1DM. Supplementation with omega-3 fatty acids among paediatric T1DM with diabetic nephropathy has been shown to improve glucose control, dyslipidaemia, delay disease progression and atherosclerosis, most likely related to their anti-inflammatory effect.

iv. Vitamin D is known for its pleiotropic effect in humans including the immune system. It shifts the T-cell response toward downregulation of the T-helper-1 immune response explaining the protective effect in T1DM which is primarily T1 mediated destruction of pancreatic β-cells. Studies have demonstrated low levels of Vitamin D in the third trimester of pregnancy may be associated with a higher risk of developing diabetes in the offspring. However, the role of Vitamin D supplementation in reducing the risk of T1D remains under investigation, with mixed results from various studies.

ROLE OF ENVIRONMENTAL CONTAMINANTS

There is growing evidence on the link between various environmental contaminants and T1DM based on epidemiological studies

i. Exposure to air pollutants such as particulate matter 2.5 and 10, ozone in the prenatal and childhood period are linked with the development of T1DM.
ii. Endocrine disrupting chemicals

(EDCs) are exogenous chemicals that interfere with hormone action. These include perfluoroalkyl substances (PFASs), pesticides, arsenic, bisphenol A (BPA) and phthalates. These studies have shown an association between the incidence of T1DM, antibody positivity and the level of these contaminants.

Exposures to these pollutants have multiple effects on the pathogenesis of T1DM such as direct effect on the immune system and the development of autoimmunity, as well as the function and survival of beta cells. Although early life exposures may be critical, even low dose continuous exposure may also contribute to the occurrence of T1DM. These findings highlight the potential for prevention of T1DM as well as adoption of environmental policies to reduce exposure to these pollutants particularly among the vulnerable population.

OTHER ENVIRONMENTAL DETERMINANTS

i. Vaccines have been linked with autoimmunity however the data is insufficient to implicate in the causation of T1DM. Some studies have shown protective effect of Rotavirus vaccination while others demonstrated no effect in the risk of T1DM.

ii. Climate and latitude are important determinants for the risk of T1D and its incidence. Studies have shown a higher incidence of T1DM in the autumn and winter season as well as countries that are farther from the equator such as the Scandinavian region. This has been attributed to temperature, ultraviolet B exposure and vitamin D status as well as effect on the circadian rhythm.

CONCLUSION

T1DM is a chronic disease with a significant burden on the community as well as the individual. The rapid increase in the incidence of T1DM poses a challenge to the global health sector as well as the country. Identifying risk factors with the potential for intervention and mitigating the risk of T1DM is the need of the hour. In this context, understanding the role of environmental factors provides us the opportunity for prevention as well as delaying the risk of T1DM. The role of epigenetics and "epidrugs" presents a novel area of research aimed at prevention and treatment of T1DM in addition to insulin.

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Chapter 05

Epidemiological Perspective of Non-autoimmune Diabetes in young people in North East India

Anupam Dutta
Sanjeeb Kakati

INTRODUCTION

Diabetes mellitus is a highly heterogeneous disorder characterized by chronic hyperglycaemia resulting from varying degrees of insulin deficiency, insulin resistance, or both. While in most high-income settings, young-onset diabetes is dominated by autoimmune type 1 diabetes or obesity-driven insulin-resistant type 2 diabetes, recent evidence suggests that in low- and middle-income countries (LMICs), a significant subset of young individuals develop diabetes that cannot be explained by these two classical pathways. South and Southeast Asia, in particular, have emerged as global epicentres of atypical, lean, non-autoimmune diabetes with distinct pathophysiological underpinnings. India alone harbours over 100 million adults with diabetes, yet the proportion of young individuals who are lean, non-autoimmune, and display early β-cell failure remains strikingly high compared with Western populations. Historically, the Indian diabetes phenotype has been described as "thin-fat"—an anthropometric paradox wherein individuals exhibit relatively low BMI but disproportionately high visceral and truncal adiposity. This phenotype, believed to originate from foetal and early-life under-nutrition followed by nutritional transitions in adulthood, confers metabolic risk even in the absence of obesity. Studies from southern and western India have suggested that a large proportion of young adults with diabetes are not overweight, and instead manifest early β-cell exhaustion rather than classical insulin resistance. However, the heterogeneity within India—across geography, ethnicity, and socio-economic context—remains under-studied. The North-East, with its largely rural, multi-ethnic population, limited healthcare access, and high burden of stunting and anaemia, provides a distinctive window into the role of under-nutrition in the pathogenesis of diabetes. The state of Assam, in the north-eastern region of India, represents a unique socio-nutritional milieu where multi-generational under-nutrition, low body-mass indices, and poverty coexist with an emerging epidemic of diabetes.

PATHOPHYSIOLOGY AND THERAPEUTIC CONSEQUENCES

Historically, the World Health Organization had proposed a category of "Malnutrition-Related Diabetes Mellitus (MRDM)" in the 1980s, later abandoned due to lack of mechanistic clarity. The Assam data revive this concept in modern form: chronic nutritional deprivation, stunting, and thin-fat body composition lead to reduced β-cell mass, diminished insulin secretory reserve, and early hyperglycaemia. The phenotype is biochemically type 2 but mechanistically closer to a nutrition-driven β-cell failure model.

From a developmental perspective, this aligns with the "thrifty phenotype" hypothesis proposed by Hales and Barker—wherein foetal under-nutrition induces adaptive β-cell and muscle programming

that becomes maladaptive under adult metabolic stress.

However, the GAD-negative, non-ketotic diabetes patients show that a large proportion belong to a distinct non-autoimmune, non-insulin-resistant category. Accurate classification using C-peptide assays and antibody panels is therefore essential for individualized treatment planning. The dominance of β-cell failure has profound therapeutic implications. Lifestyle interventions aimed primarily at reducing insulin resistance may have limited impact in such lean, insulin-deficient individuals. Early initiation of insulin or β-cell-preserving agents such as GLP-1 receptor agonists or DPP-4 inhibitors may be more appropriate than metformin monotherapy, which targets insulin sensitivity. Moreover, weight-loss recommendations must be tempered in patients already lean or under-nourished; emphasis should instead be on balanced nutrition and avoidance of further catabolism.

CLINICAL EVIDENCE IN NORTH EAST INDIA

The rationale for focusing on non-autoimmune diabetes stemmed from accumulating evidence that the majority of young Indian patients presenting with diabetes are negative for β-cell autoantibodies, such as GAD-65, and lack the typical features of autoimmune type 1 diabetes. Moreover, in contrast to the Western paradigm where young-onset type 2 diabetes is almost always obesity-related, Indian patients frequently present with normal or even sub-normal body weight. The rationale for focusing on non-autoimmune diabetes stemmed from accumulating evidence that the majority of young Indian patients presenting with diabetes are negative for β-cell autoantibodies, such as GAD-65, and lack the typical features of autoimmune type 1 diabetes. Moreover, in contrast to the Western paradigm where young-onset type 2 diabetes is almost always obesity-related, Indian patients frequently present with normal or even sub-normal body weight. Previous population-based studies such as the ICMR-INDIAB and other regional surveys have highlighted the growing prevalence of type 2 diabetes in the North-East, but they largely lacked detailed phenotypic and metabolic characterization.

One recent study from Assam, the one of the most populous state of North East India was therefore designed to address this gap and was named as the PHENOEINDY-2 study (Phenotypic and Endocrine Investigations in Non-autoimmune Diabetes in Young Indians). The specific focus was to delineate the clinical, anthropometric, and metabolic features of young adults with non-autoimmune diabetes from Assam, to distinguish insulin-secretory defects from insulin-resistance-driven disease, and to identify the contribution of under-nutrition and body composition to disease expression. This raised the hypothesis that in under-nourished environments such as Assam, the primary defect may be in pancreatic β-cell development and function, potentially rooted in foetal or early-life nutritional deprivation, compounded by later metabolic stress. Such β-cell deficiency could lead to hyperglycaemia even in the absence of substantial insulin resistance, creating a phenotype of "non-autoimmune, insulin-deficient diabetes.

In the PHENOEINDY-2 study, among 240 diabetic participants diagnosed before age 40, nearly 70 % were lean (BMI < 25 kg/m²) and about 14 % were frankly underweight (BMI < 18.5 kg/m²). Despite low BMI, dual-energy X-ray absorptiometry (DXA) revealed disproportionately high fat percentages, particularly in the trunk region. Over half of diabetic participants (53 %) had adiposity exceeding the conventional body-fat cut-offs (> 25 % in men, > 35 % in women). This confirms the "thin-fat" paradigm: lower absolute body weight but higher relative adiposity and central fat accumulation. The coexistence of low BMI and high truncal fat may explain why even modest weight gain could precipitate metabolic decompensation in such

individuals. The metabolic data reinforce the predominance of β-cell dysfunction over insulin resistance. Median fasting C-peptide levels were low, and HOMA-B (homeostatic model estimate of β-cell function) values averaged around 25, signifying markedly impaired insulin secretory capacity. In contrast, HOMA-S (insulin sensitivity) values were largely within the normal range, suggesting that insulin resistance—though present in some overweight individuals—was not the main driver of hyperglycaemia in the cohort. In the analysis, the investigators applied the Ahlqvist five-cluster framework originally derived from Scandinavian data. Nearly two-thirds of the Assamese cohort fit into the Severe Insulin-Deficient Diabetes (SIDD) subgroup, characterized by early onset, low BMI, high HbA1c, and minimal insulin resistance. Only a small fraction exhibited features of Severe Insulin-Resistant Diabetes (SIRD), and the rest distributed among the milder obesity-related or age-related clusters. This distribution differs sharply from Western or urban Indian cohorts, where SIRD and MOD (mild obesity-related diabetes) dominate. The clustering outcome underscores that the Assamese pattern of young-onset diabetes is overwhelmingly insulin-deficiency driven rather than insulin-resistance driven.

HYPOTHESIS OF UNDER-NUTRITION, STUNTING AND B CELL DYSFUNCTION

Early-life under-nutrition impairs pancreatic development and limits β-cell mass, predisposing to adult-onset diabetes even without obesity. The presence of anaemia in these patients adds another dimension: chronic micronutrient deficiencies, especially iron and B-vitamins, may contribute to β-cell oxidative stress and impaired insulin secretion. Together, these findings suggest a continuum linking malnutrition and β-cell exhaustion—a pathophysiological pathway distinct from the "overnutrition-induced insulin resistance" that defines typical type 2 diabetes. The disproportionate adiposity in lean bodies likely originates from developmental and epigenetic programming—foetal growth restriction followed by catch-up fat deposition in childhood and adolescence. The resultant body composition creates a metabolic milieu where small increments in weight or visceral fat substantially raise glucose levels because β-cell reserve is already limited. Thus, what appears clinically as "lean diabetes" is actually a composite of low lean mass and high relative adiposity. Recognition of this phenotype is vital because BMI alone underestimates risk in such populations.

PUBLIC-HEALTH AND POLICY IMPLICATIONS

At a population level, the study underscores that tackling diabetes in Northeast India cannot rely solely on obesity prevention strategies. Public-health efforts must also address chronic under-nutrition, maternal health, and early-life growth. Interventions promoting balanced nutrition during childhood and adolescence could augment β-cell reserve and mitigate future diabetes risk. Screening programs should be tailored to detect diabetes even in lean individuals, as traditional risk scores based on BMI may miss a substantial proportion of cases.

A new axis of categorization—distinguishing "under-nutrition-linked β-cell-deficient diabetes" from obesity-related insulin-resistant diabetes—may provide better predictive and therapeutic guidance. This re-conceptualization also aligns with the WHO's renewed focus on nutrition-sensitive non-communicable disease prevention in resource-limited settings.

CONCLUSION

Clinicians, researchers, and policymakers must therefore broaden their conceptual framework beyond the binary of type 1 and type 2 diabetes, recognising the continuum that includes malnutrition-related β-cell-deficient diabetes. Addressing this will require not only therapeutic innovation but also upstream interventions in nutrition, maternal health, and early childhood

development. The North Eastern experience vividly illustrates that the roots of diabetes in developing nations lie as much in deprivation as in excess—underscoring the need for a dual strategy that combats both under- and over-nutrition to curb the diabetes epidemic of the future. Future research should integrate genetic, epigenetic, and nutritional biomarkers to unravel mechanisms linking under-nutrition to β-cell dysfunction.

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Section 03

Section Editor : **Suranjit Barua**

Etiopathogenesis of Diabetes Mellitus

Chapter 06

Cellular vs Humoral Autoimmunity in Pathogenesis of Type 1 Diabetes

Arjun Baidya
Niladri Das

INTRODUCTION

Type 1 diabetes mellitus is one of the most thoroughly studied autoimmune disorders. Initial reports from the mid-20th century highlighted pancreatic pathology, noting lymphocytic infiltration of islets in newly diagnosed individuals—a phenomenon subsequently termed insulitis. This finding was pivotal, indicating that immune cells, rather than β cells alone, play a fundamental role in disease pathogenesis. Type 1 diabetes mellitus (T1D) is an autoimmune condition characterized by immune-mediated destruction of pancreatic β cells, resulting in lifelong insulin therapy. For decades the field has debated the relative contributions of cellular (T cell–mediated) and humoral (B cell / autoantibody–mediated) immunity to disease initiation and progression. Current evidences support a model in which autoreactive T cells are the proximate effectors of β-cell killing, while B cells and circulating autoantibodies plays the roles as modulators of the autoimmune process and as biomarkers.

During the 1970s and 1980s, advances in immunological techniques leads to the identification of islet-associated autoantibodies such as insulin autoantibodies (IAA), insulinoma-associated antigen 2 (IA-2) antibodies, glutamic acid decarboxylase 65 (GAD65) antibodies and later zinc transporter 8 (ZnT8) antibodies. These markers have shown effectiveness in predicting disease onset. Concurrent studies using animal models, notably the non-obese diabetic (NOD) mouse, demonstrated that the transfer of autoreactive T cells could induce diabetes, thus strongly supporting the role of cellular immunity.This evidence sparked debate over whether T1D should be classified by cellular autoimmunity involving autoreactive T cells or humoral autoimmunity marked by islet autoantibodies. The prevailing consensus acknowledges contributions from both arms of the immune system, with T cells serving as principal mediators of β-cell destruction, while B cells and autoantibodies facilitate antigen presentation, immune system amplification, and offer valuable clinical predictive utility.

CELLULAR IMMUNITY: T CELLS AS PRIMARY EFFECTORS

The most compelling evidence for cellular immunity comes from CD8+ cytotoxic T cells. Histopathological analyses of human insulitis lesions consistently show CD8+ cells as the dominant infiltrating lymphocyte population, often in direct contact with β cells. These T cells recognize β-cell peptides presented on HLA class I molecules, enabling targeted killing through perforin, granzymes, and Fas–FasL pathways. Antigen-specific CD8+ T cells targeting preproinsulin, insulin, IGRP, and other autoantigens have been found in the blood and pancreas of T1D patients. Their clonal expansion patterns indicate antigen-driven selection.

CD4+ T cells play a crucial role in orchestrating immune responses. They provide "help" for B-cell maturation and autoantibody production, and also support CD8+ cytotoxic T cells through cytokine secretion. CD4+ T cells reactive to GAD65 and IA-2 are detectable in at-risk and diagnosed individuals. In NOD mice, depletion of CD4+ T cells prevents disease, underscoring their necessity in disease initiation. Further-more, Th1-type CD4+ cells secrete IFN-γ and TNF-α, both implicated in β-cell stress and apoptosis. Th17 cells have also been detected, suggesting multiple helper lineages may contribute to disease.

A key component of T-cell biology in T1D is impaired tolerance. Regulatory T cells, defined by expression of FOXP3, normally suppress autoreactive responses. In both NOD mice and humans with T1D, quantitative or functional Treg defects have been observed. This leads to impaired immune regulation and advancing autoimmunity. Genetic polymorphisms in IL2RA and CTLA4, both critical for Treg function, further highlight the importance of defective regulation.

Cytokines such as IFN-α, IL-1β, and TNF-α, produced by innate immune cells, create an inflammatory milieu in islets. This environment facilitates antigen presentation, increases HLA expression on β cells, and promotes T-cell recruitment. Macrophages and dendritic cells act as antigen-presenting cells that link innate and adaptive immunity.

Together, these mechanisms show that cellular immunity is the final effector responsible for β-cell destruction, with CD8+ T cells playing a starring role.

HUMORAL IMMUNITY: B CELLS AND AUTOANTIBODIES

Unlike cellular responses, autoantibodies are accessible and measurable in blood, making them crucial clinical tools. (3) Four major autoantibodies are recognized:

- Insulin autoantibodies (IAA): Earliest to appear, especially in young children.
- GAD65 antibodies: Common in both children and adults, sometimes persisting long after diagnosis.
- IA-2 antibodies: Associated with more rapid disease progression.
- ZnT8 antibodies: Provide additional predictive power in autoantibody-negative cases.

Longitudinal studies show that individuals positive for two or more autoantibodies have a >70% lifetime risk of developing T1D, making these markers essential in staging preclinical disease.

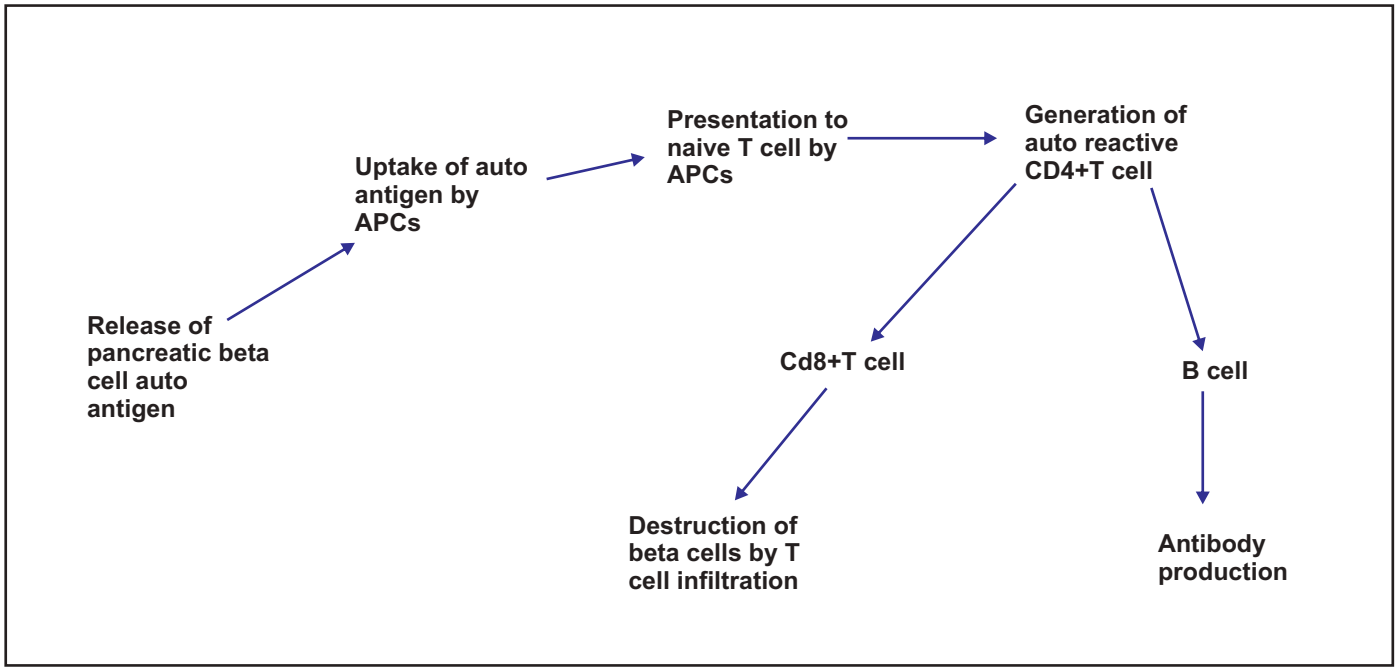
Beyond antibody production, B cells have central roles in antigen presentation. By internalizing islet antigens via their B-cell receptors, B cells efficiently present peptides to CD4+ T cells. This function provides cognate help for autoreactive T cells and sustains autoimmunity. In NOD mice, genetic or antibody-mediated depletion of B cells prevents or delays diabetes, highlighting their role in disease propagation. Human trials with rituximab, a CD20-depleting antibody, showed transient preservation of C-peptide, affirming B-cell contribution. B cells also secrete cytokines such as IL-6 and IL-10, which shape T-cell responses. Dysregulation of these pathways may skew the immune balance toward pro-inflammatory responses, further enabling β-cell autoimmunity.

INTERPLAY BETWEEN CELLULAR AND HUMORAL IMMUNITY

T1D is best understood not as a disease of "either-or" immunity but as a complex interplay: (Fig 1)

1. Environmental factors such as viral infections, microbiome alterations, or dietary exposures can cause β-cell stress and lead to antigen release.
2. B cells and dendritic cells capture and present β-cell antigens.

Figure 1: Inter-play between cellular and humoral immunity in pathogenesis of Type 1 DM



This cooperative cycle explains why both T-cell–directed (teplizumab) and B-cell–directed (rituximab) therapies can modify disease, albeit incompletely.

3. CD4+ helper T cells activate both CD8+ cytotoxic T cells and B cells.
4. Activated B cells differentiate into plasma cells, generating islet autoantibodies.
5. CD8+ T cells infiltrate islets and destroy β cells, while autoantibodies enhance immune detection without causing direct cell death.

EVIDENCE FROM IMMUNOTHERAPY TRIALS

Therapeutic attempts to modulate immune responses in T1DM provide valuable mechanistic insights into the relative contributions of cellular and humoral autoimmunity. Over the past three decades, a spectrum of immunotherapies has been tested, ranging from broad immunosuppression to targeted biologics, with varying efficacy.

Anti-CD3 Monoclonal Antibodies (Teplizumab)

Anti-CD3 therapy has been among the most successful in altering T1DM course. Teplizumab, a humanized Fc receptor–nonbinding anti-CD3 monoclonal antibody, has been shown in studies to delay the progression from stage 2 (autoantibody-positive, dysglycemia) to overt T1DM by a median of two years. This provides evidence for the involvement of T-cell–mediated autoimmunity, as CD3 is expressed on all T lymphocytes and its modulation affects the balance between effector and regulatory subsets.

Anti-B-cell Therapy (Rituximab)

Rituximab, a monoclonal antibody directed against CD20, selectively targets B lymphocytes and has been evaluated in patients with newly diagnosed type 1 diabetes mellitus. Although it transiently preserved C-peptide levels for about a year, the effect was not durable. The limited benefit underscores that while B cells contribute to autoimmunity, primarily through antigen presentation and autoantibody production, they are not the sole drivers of disease. Moreover, C-peptide preservation without long-term disease modification indicates redundancy of cellular pathways independent of humoral immunity.

Costimulatory Blockade (Abatacept)

Abatacept delays T-cell activation by blocking CD80/CD86–CD28 costimulation. Abatacept slowed decline of β-cell function in new-onset patients but did not fully halt progression. This reinforces that T-cell activation is pivotal, but redundant pathways eventually bypass costimulatory blockade.

Cytokine-targeted Therapies.

Agents directed at pro-inflammatory cytokines implicated in β-cell destruction such as anti-IL-21 or low-dose IL-2 aimed at restoring Treg function are under investigation. IL-21 blockade with liraglutide further preserves β-cell function. These highlight the pathogenic importance of the inflammatory cytokine milieu, largely driven by cellular immunity.

Antigen-specific Immunotherapy.

Insulin and GAD65-based antigen therapies (oral insulin, Diamyd vaccine) aimed at inducing tolerance have shown inconsistent results. The failure of these humoral tolerance–inducing approaches to achieve robust clinical benefit underscores that simply modulating autoantibody responses is insufficient without addressing the effector T-cell component.

Anti thymocyte globulin (ATG)

ATG, as a broad polyclonal antibody, depletes CD4+ and CD8+ T cells while sparing and expanding Tregs. It can temporarily preserve β-cell function in new-onset type 1 diabetes by reducing autoreactive T cells and promoting tolerance. Due to limited benefits and side effects, it is not standard therapy, but ongoing research explores improved dosing, combinations, and patient selection.

BIOMARKERS: PREDICTION AND STRATIFICATION

Autoantibodies are widely used for prediction because they are accessible and reproducible, making them practical for screening and staging. Cellular biomarkers, such as autoreactive T-cell frequencies, regulatory T-cell functionality, and T-cell receptor sequencing, are still under investigation due to technical challenges. Combining humoral and cellular markers may improve risk assessment and support the development of targeted immunotherapies.

CONCLUSION

Type 1 diabetes mellitus is characterised by the involvement of both cellular and humoral immune responses. CD8+ T cells drive β-cell death, while B cells and autoantibodies aid in antigen presentation and amplify immune responses. Clinical trials show both are important, suggesting future therapies should target these mechanisms to achieve lasting immune tolerance and prevent β-cell loss.

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Chapter 07

Beta Cell Dysfunction vs Mitochondrial Dynamics in Type 2 Diabetes

Bikash Bhattacharjee

INTRODUCTION

Mitochondrial dysfunction in the pancreatic beta cells plays pivotal role in the pathogenesis of type 2 diabetes mellitus (T2DM) which is the most prevalent type of diabetes mellitus. Unhealthy lifestyle including unhealthy diet containing excessive carbohydrate and fat along with lack of physical activity is the main factor for global tsunami of T2DM. Excess of carbohydrate and fat in our diet along with lack of physical exercise put stress on pancreatic beta cell mitochondria and compromise their health and function. Healthy functional mitochondria in beta cell have metabolic flexibility to use both fat and carbohydrate seamlessly for ATP production. In the face of excessive nutrient, mitochondria in beta cell get overburdened and become metabolically inflexible. Metabolically inflexible mitochondria in beta cell impair electron transfer chain (ETC) leading to electron leak and increased production of reactive oxygen species (ROS). Initially antioxidant enzyme like superoxide dismutase counter ROS like superoxide but when antioxidant fail to counter, excessive ROS damage beta cell mitochondria and can lead to beta cell apoptosis. Mitochondrial dysfunction in beta cell, leads to beta cell dysfunction and beta cell apoptosis causing loss of beta cell mass leading to progression of type 2 diabetes.

INTERPLAY AND PATHOGENESIS:

Mitochondria are the power house of the cell and produce chemical energy as Adenosine Triphosphate (ATP) through cellular respiration by the process of oxidative phosphorylation. ATP also known as cellular currency is essential for cellular functions. Apart from ATP production, Mitochondria perform fatty acid synthesis, intracellular reactive oxygen species (ROS) generation, oxidative phosphorylation (OXPHOS), thermogenesis and calcium homeostasis and plays important role in cellular metabolism.

Mitochondria are dynamic organelles and can adjust and respond to different metabolic needs and functions within the cell. They undergo changing processes of fission, fusion, mitophagy and transport for signal transduction and metabolism. These dynamic processes determine the morphology, quality, quantity, distribution of mitochondria within the cell and mitochondrial functions. Mitochondria have their own DNA and need continuous repair and replacement of components for proper function. Balanced mitochondrial dynamics is essential for optimal function of mitochondria and cell fate. Mitochondrial fission is essential for mitochondrial quality control (MQC) by elimination of impaired and dysfunctional mitochondria, and promotes apoptosis under severe cellular stress. Fusion helps in exchange and mixing mitochondrial content between mitochondria to maintain mitochondrial function. Mitophagy is essential for mitochondrial quality control by selective clearance of damaged mitochondria that inhibits pro-apoptotic proteins.

Mitochondrial fission is mediated by dynamin-related protein (Drp1) which is important determinant of insulin resistance. Aerobic exercise inhibits activation of Drp1 and improves fatty acid oxidation and insulin sensitivity. Mitochondrial fusion is mediated by mitofusin (MFN) 1/2 and optic atrophy protein 1(Opa1). Apoptosis is a process of cell death and is critical for cellular homeostasis. Mitochondria play important role in the initiation of apoptosis by secreting proapoptotic molecules and chromosomal fragmentation. In mitochondrial dysfunction, OXPHOS is impaired due to impairment of electron transfer chain (ETC) proteins leading to increased production of reactive oxygen species (ROS). Increased ROS damage mitochondrial lipids, proteins and DNA (mtDNA). Mitochondrial Quality Control comes into play to maintain structural and functional integrity of the mitochondria. But, when oxidative stress becomes unmanageable, cytochrome-c is released in cytosol heralding apoptosis.

Mitochondria are the most important cellular source of ROS and studies indicate that Beta cells of patients with T2DM produce larger amount of ROS compared to nondiabetic subjects. Cardiolipin is a structurally unique phospholipid, present in the inner mitochondrial membrane for maintaining mitochondrial structure to provide support to mitochondrial proteins including Cytochrome c anchored to outer surface of the inner mitochondrial membrane. Cardiolipin is oxidized by increased mitochondrial ROS and Cytochrome c gets detached from the membrane. Subsequently, Cytochrome c participates in apoptosome formation that results in caspase-9 activation and subsequent activation of the executioner caspases 3, 6, and 7 that dismantle the cell during apoptosis. Glucose sensing in beta cells requires the coupling of glycolysis to oxidative phosphorylation in mitochondria to produce ATP. The respiratory chain complexes pump protons out of the mitochondrial matrix to generate an electrochemical proton gradient that provides the energy required by ATP synthase to produce ATP from ADP. The rise in cytoplasmic ATP/ADP ratio in beta cell induces closure of ATP sensitive potassium channels, depolarization of the plasma membrane, opening of voltage-gated calcium channels, influx of calcium and triggering of insulin exocytosis. The oxidative phosphorylation is essential to glucose-stimulated insulin secretion in beta cells. Evidences indicate that inhibition of mitochondrial chain complexes by various means, results in blockade of insulin secretion. Moreover, maternally inherited T2DM caused by mitochondrial mutation expressing defective insulin secretion, prove the essential role of mitochondria in glucose stimulated insulin secretion.

Uncoupling protein-2(UCP2), a member of mitochondrial carrier protein reduce ATP synthesis by lowering mitochondrial membrane potential. UCP2 negatively regulates insulin secretion. Obesity and chronic hyperglycemia increase mitochondrial superoxide production and this cause activation of UCP2 and results in pancreatic beta cell dysfunction.

As stated above, the integrity of phospholipid cardiolipin is important to maintain mitochondrial structure and function. Cardiolipin resides in the inner mitochondrial membrane which is also the locus of accelerated ROS production. This proximity of cardiolipin to ROS make it vulnerable to oxidation. To counteract the continuous oxidation of cardiolipin and the associated impairment of mitochondrial function, mitochondrial phospholipid gluthathione peroxidase (Gpx4) and a phospholipase A2(PLA2) eliminate oxidized fatty acids from cardiolipin. Among PLA2 family members, Group 4A PLA2(ipla2 Beta) plays important role in cardiolipin homeostasis.

UCP2 antagonism and ipla2 Beta agonism are therapeutic strategies for protecting mitochondrial beta cell structure and function. Apart from beta cell dysfunction, insulin resistance (IR) is fundamental to the development of type 2 diabetes(T2D). Metabolic studies in humans and rodents, have highlighted the

critical role of mitochondrial dysfunction as a predisposing condition for IR in skeletal muscle, white adipose tissue and liver. Mitochondria use fat for energy production by beta oxidation and subsequent bioenergetic process. Due to mitochondrial dysfunction, fat is not utilised for energy production and get deposited as ectopic fat in insulin sensitive tissues, causing insulin resistance. Intracellular lipids disrupt insulin signalling and insulin receptor substrate (IRS) undergoes serine phosphorylation instead of physiological tyrosine phosphorylation. IR is associated with decreases in insulin mediated glucose uptake in skeletal muscle with decreased glycogen synthesis. In white adipose tissue insulin signalling is compromised due to IR resulting in decreased lipogenesis and increase in lipolysis generating excess free fatty acid. Increased circulating free fatty acids causes more insulin resistance and also provide substrate for increased gluconeogenesis in liver. Insulin cannot supress hepatic glucose output due to hepatic IR. Taken together, IR in skeletal muscle, white adipose tissue and liver lead to more hyperglycemia. Moreover, hyperglycemia causes more mitochondrial dysfunction which leads to more beta cell dysfunction. So, it becomes a vicious cycle. Enhanced mitochondrial biogenesis improves ATP synthesis, facilitating insulin-stimulated glucose uptake. Insulin regulates mitochondrial quality control by suppressing mitochondrial fission and enhancing biogenesis.

Mitochondria and endoplasmic reticulum (ER) are two cellular organelles which are spatially and functionally related to each other. Dysfunction of one induces dysfunction of other. Mitochondria are in close contact with the ER through shared mitochondria associated membranes. The main function of the ER is to regulate protein folding, lipid synthesis, and calcium homeostasis. The accumulation of unfolded/misfolded proteins within the ER causes ER stress. Although the initial ER stress response is an adaptive response to restore ER function, prolonged ER stress is detrimental to the cell and impairs mitochondrial function. Similarly, low level of ROS is necessary for cellular signalling and adaptive response, but excessive ROS is detrimental to cells and impairs ER. ER play central role in insulin synthesis. Mitochondrial dysfunction along with ER stress/dysfunction are the core cellular patho- physiological defects in T2DM.

THERAPEUTIC OPTIONS AND IMPACT ON MITOCHONDRIAL DYNAMICS

Exercise is the most potent therapeutic approach for the improvement of mitochondrial health, not only in muscle but also in other tissues including endocrine pancreas. Exercise increases mitochondrial biogenesis by stimulating the production of new mitochondria. Exercise activates the signalling pathways including regulators like PGC-1Alpha, a promoter for the transcription of genes essential for mitochondrial creation. Exercise enhances mitochondrial quality control by the removal of damaged or dysfunctional mitochondria through mitophagy. Exercise improves mitochondrial dynamics by maintaining the balance between fusion and fission of mitochondria, which is crucial for maintaining their proper shape, function and distribution within the cell. So, exercise improves beta cell health and function by improving mitochondrial health. Exercise improves insulin sensitivity which also contributes to beta cell function. Healthy diet containing adequate protein, appropriate fat and carbohydrate along with micro nutrients are necessary for mitochondrial health for improving beta cell function. Diet containing excess fat and carbohydrate cause nutrient overload to the mitochondria and bring about metabolic inflexibility and dysfunction. Lifestyle modification play a key role in maintaining mitochondrial health and beta cell function.

Several glucose lowering agents exert their beneficial effect in patient with type 2 diabetes by targeting mitochondrial quality control. Metformin

efficiently prevents high glucose induced mitochondrial structural and functional abnormalities in human islets cells. It has beneficial clinical applications on promoting mitochondrial function and mitophagy in type 2 diabetic patients. SGLT2 inhibitors mitigate renal and cardiac injury by suppressing fission and enhancing mitophagy. GLP1 receptor agonist reverse cardiac mitochondrial abnormalities. Pioglitazone exert neuroprotective affects by targeting altered brain mitogenesis.

Imeglimin is a recently introduced first in class novel oral agent for the treatment of type 2 Diabetes. Underlying mechanism may involve correction of mitochondrial dysfunction. It has been observed to rebalance respiratory chain activity, resulting in reduced ROS formation.

CONCLUSION

T2DM is a lifestyle disease. Unhealthy lifestyle including lack of physical activity and nutrient overload causes mitochondrial dysfunction. Oxidative stress due to mitochondrial dysfunction, induces ER stress. Mitochondrial dysfunction and ER stress are the core cellular pathophysiological defects causing beta cell dysfunction leading to T2DM. Mitochondrial dysfunction also causes insulin resistance in muscle, adipose tissue and liver. Beta cell dysfunction and insulin resistance are the core defects producing metabolic dysfunction and hyperglycemia. Hyperglycemia causes more mitochondrial dysfunction and beta cell dysfunction. Lifestyle modification including appropriate exercise and diet is the best cost effective therapeutic intervention to improve mitochondrial function for prevention and management of T2DM.

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Chapter 08

Current Understanding of Monogenic Diabetes

Uma Kaimal Saikia
Abhijit Sarkar

INTRODUCTION

Monogenic diabetes is a heterogeneous group of disorders characterized by hyperglycaemia, most often resulting from impaired function or abnormal development of the pancreatic islets of Langerhans, particularly the insulin-secreting β-cells, with only rare involvement of the exocrine pancreas. These conditions are unified by the presence of a single pathogenic genetic alteration. Clinically, monogenic diabetes encompasses a spectrum that includes neonatal diabetes mellitus (NDM)—a rare form with an incidence of approximately 1 in 90,000 live births, typically presenting within the first six months of life , maturity-onset diabetes of the young (MODY)—classically defined as early-onset diabetes manifesting in childhood, adolescence, or young adulthood (before 25 years of age) with a strong hereditary component and often affecting multiple generations and a group of syndromic monogenic disorders such as Wolfram syndrome, Wolcott–Rallison syndrome, and Mitchell–Riley syndrome, in which diabetes (either neonatal or later onset) occurs as part of a multisystem disease, not necessarily as the initial manifestation . Monogenic diabetes also includes gene defects leading to insulin resistance such as the lipodystrophies and maternally inherited mitochondrial diabetes. Differentiation from the commoner Type 1 and Type 2 diabetes is important in guiding therapeutic modalities, follow up and identifying at risk individuals by genetic testing.

EPIDEMIOLOGY

Monogenic diabetes accounts only for a small proportion of diabetics. In the pediatric and adolescent population the prevalence ranges from 1-5% with MODY accounting for approximately 0.5–5% of non-autoimmune diabetes. The true global prevalence is likely underestimated due to limited genetic testing, low awareness, and phenotypic overlap with type 1 and type 2 diabetes. Even in high-resource settings, many cases remain undiagnosed. Advances in next-generation sequencing have improved detection, particularly in young patients with classical MODY features.

In South India, analysis of 35 monogenic diabetes genes identified a pathogenic variant in 15% of 152 patients suspected of having monogenic diabetes (onset <30 years, hyperglycaemia controlled without insulin for ≥2 years, autoantibody-negative, no ketonuria, and a three-generation family history). Compared with European populations, GCK mutations were less common, whereas HNF1A and ABCC8 variants were more frequent. Population-level data in adults remain limited. The UNITED study in the UK screened all patients diagnosed <30 years identifying monogenic diabetes in 3.6% of participants. These findings underscore the challenge of detecting cases beyond high-risk groups. A recent multi-centre Indian study reported a prevalence of

15.5% (120/774) among young-onset diabetes cases. Among MODY subtypes, HNF1A mutations were most common (32.5%), followed by HNF4A (16.7%), HNF1B, ABCC8, GCK, PDX1, and INS respectively. Syndromic forms included Wolfram syndrome followed by maternally inherited diabetes with deafness (MIDD). These data highlight the genetic and clinical heterogeneity of monogenic diabetes in India and emphasize the importance of systematic genetic testing for accurate diagnosis and management.

GENETIC BASIS AND PATHOPHYSIOLOGY

Human pancreatic islets consist of approximately 60% β-cells (insulin-secreting), 30% α-cells (glucagon-secreting), and 10% δ-cells (somatostatin-producing), PP cells (pancreatic polypeptide), and ε-cells (ghrelin-producing). These endocrine cells are randomly interspersed within the islets. In β-cells, insulin is stored in secretory granules and released in response to elevated glucose, neurotransmitters, and incretin hormones. Disruption of β-cell development or function underlies the pathophysiology of monogenic diabetes. The inheritance of MODY is predominantly autosomal dominant, whereas neonatal diabetes and syndromic forms may follow either dominant or recessive patterns. Many monogenic diabetes genes encode transcription factors highly expressed in pancreatic islets and β-cells. HNF1A is the most frequently mutated, causing MODY or adult-onset non-autoimmune diabetes; mutations impair DNA binding, transactivation, protein expression, and nuclear localization, disrupting β-cell function and insulin transcription. Biallelic PDX1 or PTF1A deficiencies and heterozygous GATA6 mutations cause neonatal diabetes with pancreatic agenesis and extra-pancreatic manifestations. These transcription factors are essential for pancreatic development and cell fate specification, although PTF1A is expressed only during early pancreatic development, regulating exocrine versus endocrine lineage.

Several genes encode channel subunits (ABCC8, KCNJ11, KCNK16) or transporters (SLC2A2, SLC19A2). ABCC8 and KCNJ11 form the ATP-sensitive potassium channel, which links glucose metabolism to insulin secretion. Gain-of-function mutations in these genes keep the channel open, inhibiting insulin release and causing neonatal diabetes, MODY, or late-onset diabetes. KCNK16, expressed exclusively in β-cells, encodes another potassium channel; activating mutations increase potassium current, disrupt calcium flux, and reduce glucose-stimulated insulin secretion, leading to MODY. Rare mutations in SLC2A2 and SLC19A2 cause syndromic forms, including Fanconi–Bickel syndrome and Rogers syndrome, with multi-organ involvement. In the cytosol, GCK, encoding glucokinase, is the most frequently mutated gene in dominantly inherited monogenic diabetes. GCK catalyses glucose phosphorylation in β-cells and hepatocytes. MODY-associated GCK mutations impair enzymatic activity leading to reduced glycolytic flux, defective glucose sensing, and a rightward shift in glucose-stimulated insulin secretion.

CLINICAL PRESENTATION AND DIAGNOSIS

The American Diabetes Association (ADA) recommends that all infants diagnosed with diabetes within the first six months of life, or individuals who later report a diagnosis at or before six months of age, undergo immediate genetic testing for neonatal diabetes, a form of monogenic diabetes. Furthermore, genetic testing should be considered in children and in young adults whose diabetes is not characteristic of type 1 or type 2 diabetes, particularly when the condition is observed across successive generations, suggesting an autosomal dominant pattern of inheritance consistent with MODY. MODY has several clinical clues that help distinguish it from type 1 and type 2 diabetes. The onset of hyperglycaemia is usually in adolescence or

young adulthood, often before 35 years of age, and many patients have a strong family history of diabetes in successive generations, reflecting its autosomal dominant inheritance. Some gene-specific features can be striking—for example, HNF4A-MODY may initially present with transient neonatal hypoglycaemia due to hyperinsulinism, with diabetes developing later in life.

The phenotype is often atypical for type 1 diabetes: patients generally lack pancreatic autoantibodies when tested at diagnosis, require relatively low doses of insulin (<0.5 U/kg/day) if insulin is used, and continue to show evidence of endogenous insulin secretion long after the "honeymoon" phase, as demonstrated by a detectable C-peptide (>0.6 ng/mL or >0.2 nmol/L) several years after diagnosis. They rarely develop ketoacidosis, even when insulin therapy is interrupted.

Features inconsistent with type 2 diabetes are equally important. MODY patients tend to be non-obese or lean, lack stigmata of insulin resistance such as acanthosis nigricans, and may show a lipid profile unlike that typically seen in type 2 diabetes. For instance, HNF1A-MODY is associated with normal triglycerides and relatively high HDL cholesterol. Other characteristic patterns include mild, stable fasting hyperglycaemia, especially in GCK-MODY, and a marked sensitivity to sulfonylureas in HNF1A- and HNF4A-MODY. Extra pancreatic features may also provide diagnostic hints, such as renal, hepatic, or gastrointestinal involvement depending on the underlying mutation.

Family history is often the most telling feature. Unlike type 1 diabetes, which is sporadic in most cases (only about 2–6% have an affected parent), and type 2 diabetes, which tends to occur in the context of obesity and later age of onset, MODY typically presents as early-onset diabetes in lean individuals with a clear vertical inheritance pattern. A detailed three-generation family history—focusing on age at onset, body habitus, treatment requirements, and inheritance pattern—helps distinguish MODY from type 2 diabetes. Initial evaluation for suspected MODY should include fasting glucose, HbA1c, C-peptide, and at least three islet autoantibodies (GADA, IA-2A, ZnT8), ideally at diagnosis. Antibody testing is the most cost-effective way to exclude type 1 diabetes before proceeding to genetic testing, while persistence of C-peptide (>0.6 ng/mL) beyond 3–5 years supports MODY over type 1. Additional tools include the University of Exeter MODY probability calculator (post-test probability >25% suggests genetic testing), though its performance is best validated in White European populations and less accurate in South Asians. Non-invasive tests such as urinary C-peptide/creatinine ratio (UCPCR) and hsCRP may further help distinguish MODY subtypes, but require broader validation before being adopted as standard care.

Molecular genetic testing is recommended and cost-effective for all patients suspected of monogenic diabetes or MODY. Targeted approaches include serial single-gene or multigene panel testing, while comprehensive genomic methods include chromosomal microarray and exome sequencing. If the phenotype is clearly consistent with GCK-MODY, single-gene testing is usually sufficient. When the phenotype is ambiguous or difficult to distinguish from other MODY forms, a MODY multigene panel covering common and validated genes is preferred, with chromosomal microarray analysis in selected scenarios. Large deletions in HNF1B, such as the 17q12 recurrent deletion syndrome, are associated with distinct phenotypes and can be detected and characterized using multigene panels. If a genetic cause remains unidentified or additional clinical features are present, referral to a specialty centre and exome sequencing should be considered. Overall, the cost-effectiveness of testing depends on local availability and pricing.

TREATMENT OF MONOGENIC DIABETES

The optimal treatment of young patients with MODY has evolved considerably over the decades. In the 1970s and 1980s, most children with hyperglycaemia were treated with insulin, regardless of aetiology. This included patients with GCK-MODY, many of whom received daily insulin injections unnecessarily, with minimal benefit. By the early 1990s, it became clear that MODY was heterogeneous, with some patients responding well to sulfonylureas while others did not.

Dominant GCK-Diabetes

Treatment of GCK-deficient patients is generally unnecessary. Blood glucose is tightly regulated by GCK enzymatic activity, and these patients do not develop classical diabetes complications, such as retinopathy or nephropathy. Discontinuation of glucose-lowering therapy does not alter glycaemic control or clinical outcomes, regardless of prior treatment duration. Mild fasting hyperglycaemia in asymptomatic individuals should therefore be monitored without pharmacological intervention. Pregnancy requires special consideration. When a mother with a pathogenic GCK mutation carries a fetus that does not inherit the mutation, maternal hyperglycaemia can induce fetal hyperinsulinemia and increase the risk of macrosomia. If both mother and fetus share the mutation, maternal and fetal glucose thresholds are aligned, resulting in normal fetal insulin levels and birthweight. When the father is GCK-deficient and the fetus inherits the mutation while the mother is normoglycemic, low maternal glucose may impair fetal insulin secretion, leading to low birthweight. If the fetus does not inherit the paternal mutation, fetal insulin secretion and growth remain normal.

Insulin therapy during pregnancy should be reserved for frank maternal hyperglycaemia or evidence of accelerated fetal growth on ultrasonography. Dominant GCK-diabetes should be suspected in pregnant women with mild fasting hyperglycaemia (5.6–8.0 mmol/L), particularly in the first trimester and in those with a normal body mass index. Other clues include a history of gestational diabetes, persistent mild hyperglycaemia before conception or postpartum, a strong family history of early-onset type 2 diabetes, fetal macrosomia, or insulin therapy only during a prior pregnancy that was discontinued after delivery. Identifying GCK mutations in pregnant women is critical, as optimal diabetes management depends primarily on the fetal genotype rather than maternal glycaemia. Approximately 5% of women with gestational diabetes carry a pathogenic MODY mutation, although systematic genetic screening remains limited.

HNF1A and HNF4A Diabetes

Mutations in HNF1A or HNF4A impair insulin secretion, causing early-onset diabetes often revealed at puberty. Early recognition is crucial, as these patients respond exceptionally well to low-dose sulfonylureas due to enhanced insulin sensitivity and altered hepatic metabolism. The efficacy of sulfonylureas depends on residual insulin secretion (C-peptide), BMI, disease duration, and HbA1c, while GLP-1 receptor agonists may be considered if sulfonylureas are insufficient.

During pregnancy, maternal glycaemic control and foetal mutation status influence foetal growth. Sulfonylureas cross the placenta, potentially causing macrosomia and hyper-insulinemic hypoglycaemia, particularly in the third trimester; switching to insulin before pregnancy—or by the end of the first trimester—is recommended. Foetal growth should be monitored via ultrasonography every 2 weeks from 28 weeks, with induction or Caesarean delivery between 35–38 weeks if macrosomia develops. Additionally, HNF1A-diabetes may be associated with liver adenomatosis (~6.5% of cases), warranting screening in affected families.

KCNJ11- and ABCC8-Diabetes

Heterozygous activating mutations in KCNJ11 and ABCC8 can cause neonatal diabetes, MODY, or even

typical T2DM. High-dose sulfonylureas are the treatment of choice, targeting SUR1 (encoded by ABCC8), and provide excellent long-term glucose control. Successful transition from insulin to sulfonylureas depends on the specific mutant channel's in vitro response and diabetes duration, emphasizing the importance of early genetic diagnosis. Many patients also exhibit neurological features—epilepsy, hypotonia, cognitive or motor impairments, and attention deficits—with earlier sulfonylurea therapy shown to improve neurological outcomes, especially hypotonia.

Most other forms, including HNF1B-diabetes, lack specific targeted treatments and are usually managed with insulin therapy, as sulfonylureas are generally ineffective, likely due to pancreatic atrophy and hepatic insulin resistance. Genetic diagnosis is critical for monitoring extra-pancreatic manifestations, such as cardiac defects in GATA4/6 mutations and renal or genitourinary abnormalities in HNF1B mutations. Lifestyle and dietary recommendations align with those for T1DM and T2DM, emphasizing balanced nutrition and regular physical activity, while weight loss is typically unnecessary as most patients are non-obese.

INDIAN PERSPECTIVES

India has established a national monogenic diabetes registry to support long-term studies, genetic counselling, family screening, and personalized therapy. Increasing use of next-generation sequencing (NGS), including targeted panels and whole-exome sequencing, has improved diagnostic accuracy. These integrated efforts position India as a leader in precision medicine for monogenic diabetes in the Asian context.

FUTURE DIRECTIONS

The field of monogenic diabetes is rapidly evolving. Advances in genomic technologies, particularly the routine integration of next-generation sequencing and whole-exome or whole-genome sequencing, are expected to broaden diagnostic coverage and reduce costs. Emerging therapeutic avenues include gene-based interventions such as CRISPR-Cas9–mediated genome editing, as well as small-molecule modulators targeting specific ion channel defects. Stem cell–based approaches, including the use of patient-derived induced pluripotent stem cells, are being actively explored both for disease modelling and for potential regenerative therapies. Beyond its immediate clinical implications, monogenic diabetes continues to serve as a paradigm for precision medicine. It illustrates how genetic diagnosis not only alters treatment but also informs prognosis, guides family planning, and enables the study of broader mechanisms underlying β-cell biology and diabetes pathogenesis.

CONCLUSION

Monogenic diabetes, though uncommon, exemplifies the transformative impact of precision medicine in endocrinology. The growing availability of genetic testing, particularly in countries such as India where early-onset diabetes is common, is bridging the diagnostic gap and preventing unnecessary or inappropriate treatment. As genomics, advanced therapeutics, and translational research continue to evolve, the management of monogenic diabetes will become increasingly individualized, with lessons that extend far beyond this rare group of disorders to the wider field of metabolic disease.

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Chapter 09

Role of Hyperglycemia in Complications of Diabetes and Determinants of Individual Susceptibility

Ksh. Achouba Singh

INTRODUCTION

Diabetes is one of the most precarious disease that humankind have come to face in recent times.

It is a chronic health condition that affects how the body turns food into energy, primarily involving problems with the hormone insulin. It occurs when the body either does not produce enough insulin or cannot effectively use the insulin it produces, leading to high levels of glucose in the blood.

There are diverse types of diabetes, including type 1, type 2, and gestational diabetes, each with distinct causes and management approaches. The prevalence of diabetes mellitus is increasing worldwide at an alarming rate due to population growth, obesity, sedentary lifestyle and aging. Consequently, diabetic complications are also on the rise. Left untreated or poorly managed, diabetes can lead to serious complications such as heart disease, kidney damage, vision problems, and nerve damage. However, with early diagnosis, healthy lifestyle choices, medical care, and consistent monitoring, diabetes can be managed effectively, allowing individuals to lead healthy and active lives.

We shall focus more on how hyperglycemia or high blood glucose levels determine directly or indirectly the sequelae of various complications of Diabetes and how Individual predispositions changes the disease progress in individuals. The basic causes of complications include tissue metabolism disorders caused by chronic hyperglycemia, which results in damage to many organs.

PATHOGENESIS OF THE DISEASE COMPLICATIONS

Glucose homeostasis is maintained by the highly coordinated interaction of three physiologic processes: insulin secretion, tissue glucose uptake and hepatic glucose production. Glucose homeostasis is controlled primarily by the anabolic hormone insulin and by some insulin-like growth factors. Several catabolic hormones (glucagons, catecholamines, cortisol, growth hormone, and adrenocorticotropic hormone) may antagonize the action of insulin and are known as anti-insulin or counter-regulatory hormones. It is often found that critically ill patients incur hyperglycemia because of insulin resistance even if it is not complicated by diabetes.

Patients with diabetes are more susceptible to stress and when it occurs, insulin resistance and an insulin secretion decrease result from the response to stress by the neuroendocrine system because secretion of anti-insulin hormones is enhanced. This leads to enhancement of glucogenesis in the liver, of lipolysis in adipose tissue, and of protein catabolism in skeletal muscle.

Chronic Hyperglycemia can lead to creation of **reactive oxygen species (ROS)** such as superoxides (O_2^-), hydroxyl radicals (OH^-), peroxyl radicals (ROO^-) or nitric oxide. ROS are generally involved in

a diversity of biological phenomena, such as inflammation, carcinogenesis, aging, and atherosclerosis. However, several antioxidant enzymes help to maintain low levels of ROS.

Oxidative stress occurs when this balance is skewed. This then damages cellular components, such as lipids, proteins or DNA which further leads to origin of complications of diabetes. It is reported that 8-hydroxy-2-deoxyguanosine (8-OHdG), which is an indicator of oxidative damage of DNA, increases in patients with type 2 diabetes mellitus, and that 8-OHdG, 4-hydroxy-2-nonenal and heme oxygenase-1, all oxidative stress markers, increase in the pancreatic islet cells of type 2 diabetes mellitus animal models.

ROS are generated in hyperglycemia through 3 known pathways –

1. A non-enzymatic glycosylation reaction (glycation) of various structures take place which lead to the creation of an Amadori Compound which further leads to the creation of metabolites known as Advanced Glycation End products (AGEs). These AGEs are instrumental in the formation of ROS.
2. ROS is produced as an intermediate product from oxygen in the Electron Transport Chain (ETC) of the mitochondrias inside our cells. When hyperglycemia occurs, more fuel in the form of glucose is then available to the cell and ETC to create more ATPs and ROS.
3. Hexosamine Pathway leads to the formation of glucosamine which can further cause ROS generation and Oxidative stress in general. This particular cycle is enhanced in diabetic states.

ROS generated here then brings about Reduction of Insulin Biosynthesis and Increase in Insulin Resistance in the body. Biosynthesis of insulin decreases when pancreatic β-cells are exposed to chronic hyperglycemia in animal models of type 2 diabetes mellitus, and a similar phenomenon was induced by oxidative stress caused in the diabetic state. In other words, promoter activity of the insulin gene and mRNA expression decrease, and insulin gene expression is thus inhibited. It was also found that the DNA binding capacity of Pancreatic duodenal homeobox-1 (PDX-1), which is an important transcription factor for insulin genes, decreases. The use of antioxidant drugs resulted in an improvement of insulin secretion capacity as well as an increase in insulin mRNA expression. On the other hand, it was also found that oxidative stress and activation of the c-Jun N-terminal kinase pathway are involved in a decline in insulin biosynthesis and secretion due to chronic hyperglycemia.

Glucotoxicity also takes part in insulin resistance of insulin-sensitive tissues, which include liver, skeletal muscle, and adipose tissue. Insulin resistance has been shown to be present before the onset of chronic hyperglycemia, although the latter may contribute to aggravation of the diabetic state by increasing insulin resistance. It is known that incubation of primary adipocyte cells with chronic high glucose concentration can induce oxidative stress. Moreover, it was demonstrated that oxidative stress induces insulin resistance in the 3T3-L1 adipocyte cell line by inhibiting the translocation of Glut 4 to the plasma membrane.

COMPLICATIONS OF DIABETES

Chronic complications are of two types

1. **Micro-vascular** diseases
2. **Macro-vascular** diseases

Micro-vascular complications are retinopathy, neuropathy or nephropathy. The retina is extremely sensitive to oxidative stress since it has higher oxygen uptake and glucose oxidation than any other tissue. Studies of diabetic rat retina and retinal cells incubated with a high concentration of glucose have shown that the concentration of superoxides is elevated. It has been demonstrated in animal models that oxidative stress is not only involved in the development of retinopathy but also in the

persistence of the pathology after normalization of glucose concentration, as the result of persistent ROS. Oxidative stress is also strongly suspected to be involved in the development of diabetic neuropathy. Several studies have shown the capacity of antioxidant enzymes to prevent or reverse the toxic effect of chronic hyperglycemia in the nerves. Moreover, oxidative stress may contribute to the pathogenesis of diabetic nephropathy since the presence of high concentrations of mitochondrial oxidative stress markers has been demonstrated in the urine and kidneys of diabetic rats.

Macrovascular Complications

Cardiovascular complications are the most prevalent cause of death in diabetic patients. Moreover, it has been clearly shown that chronic hyperglycemia during diabetic and pre-diabetic states is linked to an increased risk for the development of cardiovascular diseases. Long-term incubation of macro vessels with high-concentration glucose was found to strongly increase the risk of cardiovascular, cerebrovascular and peripheral arterial diseases. Activation of protein kinase C by hyperglycemia is thought to play a central role in vascular complications since it leads to: (1) modification of contractile protein function, (2) an increase in the activity of nitric oxide synthase, and (3) activation of the angiotensin-converting enzyme (ACE). Activation of ACE has been linked with apoptosis and necrosis of cardiomyocytes and endothelial cells. The importance of ACE in cardiovascular disease development was confirmed by studies showing the inhibition of ACE can protect against cardiovascular diseases. Finally, protein glycation is another factor probably involved in the development of cardiovascular diseases.

In Acute Settings, hyperglycemia can exacerbate a number of perioperative problems, including cardiac, neurologic, and infectious complications. In general, most outcomes tend to improve with treatment of hyperglycemia.

Diabetic Ketoacidosis develops when there is not enough insulin in the body. When this happens, glucose cannot enter the cells. Blood sugar level rises, and body begins to break down fat for energy. When fat is broken down for energy in the body, ketone bodies are created. Ketones accumulate in the blood and eventually spill into the urine. If it is not treated, diabetic ketoacidosis can lead to a diabetic coma that can be life-threatening.

Hyperosmolar Hyperglycemic State occurs when the insulin doesn't function properly combined with lack of proper hydration. Blood glucose levels may become very high — greater than 600 milligrams per deciliter (mg/dL), (33.3 millimoles per liter (mmol/L)) without ketoacidosis.

Glucose then goes into the urine, causing increased urination. If it is not treated, diabetic hyperosmolar hyperglycemic state can lead to life-threatening dehydration and coma.

Infection in acute complications is a clinical condition that is not specific to but can easily become complicated in diabetic states. Diabetic patients have reduced immune function and enhanced bactericidal activity, so that special attention is required since the infection focus expands much faster than in non-diabetic patients.

This becomes a problem particularly in the fields of surgery, emergency and critical care medicine. It has been confirmed that perioperative appropriate glycemic control promotes wound healing. Perioperative infectious complications, including surgical site infection, represent serious postoperative complications. Compared with non-diabetic patients, diabetic patients suffer from an increased incidence of such infections, especially surgical site infection. It was reported that patients with preoperative elevation of HbA1c levels show a significantly higher incidence of surgical site infection than patients with normal HbA1c levels. Recent basic researches have found that the functional decline of neutrophils is caused by a

hyperglycemic state, and that the mechanism of this decline includes increased adhesive capacity and diminished chemotaxis, phagocytic activity and bactericidal capacity. Neutrophilic function is reduced in proportion to an increase in the blood glucose level, and 200 mg/dL is assumed to be the threshold of neutrophil dysfunction. Furnary et al reported that the incidence of deep sternal wound infection decreased from 2.0% to 0.8% in a patient group whose blood glucose level was kept below 200 mg/dL by insulin administration, and there are other reports of reduced infectious risk due to strict glycemic control. Several recent clinical studies have demonstrated the efficacy of strict glycemic control for reducing the mortality rate of post-operative or emergency patients.

DETERMINANTS OF INDIVIDUAL SUSCEPTIBILITY

Complications of Diabetes are determined by a complex interplay of genetic, lifestyle, and environmental factors.

Genetic factors:

Type 1 diabetes- As an autoimmune disease, type 1 diabetes (T1D) is highly influenced by genetics. A person with a first-degree relative with T1D has a 15 times greater risk of developing the condition.

1. **Human Leukocyte Antigen (HLA) genes** are the strongest genetic link to T1D, accounting for about 50% of the genetic risk. Specific variants of HLA Class I and Class II genes regulate the immune system's response and are associated with a heightened risk of T1D.
2. More than 60 other genetic loci have been linked to T1D, including the PTPN22 and CTLA4 genes, which are involved in immune system regulation.

Type 2 diabetes- Type 2 diabetes (T2D) is a polygenic disorder, meaning many genes with small effects contribute to the overall risk.

1. TCF7L2 gene is the most significant and consistently replicated genetic risk factor for T2D. Variants of TCF7L2 are associated with impaired insulin secretion.
2. Additional genes linked to T2D susceptibility include FTO, which is associated with obesity, as well as KCNJ11 and SLC30A8, which affect beta-cell function and insulin storage.

Lifestyle and behavioral factors:

Lifestyle factors often act as a critical bridge between genetic predisposition and the development of diabetes, particularly for type 2.

1. Diet: An unhealthy diet, especially one high in processed foods, sugar-sweetened beverages, and refined grains, significantly increases risk. In contrast, diets rich in fiber, whole grains, fruits, and vegetables are protective.
2. Physical inactivity: A sedentary lifestyle increases insulin resistance, making it a key modifiable risk factor for T2D. Regular physical activity, such as 30 minutes of brisk walking per day, can significantly lower risk.
3. Weight: Being overweight or obese is one of the strongest risk factors for T2D. The risk increases with higher body mass index (BMI), particularly if excess fat is stored in the abdomen. Weight loss can significantly reduce diabetes risk.
4. Sleep patterns: Poor sleep quality and duration (both too short and too long) are associated with an increased risk of diabetes. Sleep disturbances can negatively affect hormonal balance and glucose metabolism.
5. Smoking and alcohol: Tobacco use and heavy alcohol consumption increase the risk of T2D. Quitting smoking can help lower this risk.

Environmental factors:

1. Built environment: Neighborhood features, such as limited access to greenspace or healthy food options ("food deserts"), can increase susceptibility to T2D.
2. Air pollution: Exposure to air pollutants, especially fine particulate matter (PM2.5), is linked to increased T2D risk.
3. Infections: For T1D, exposure to certain viruses, such as enteroviruses, may act as an environmental trigger in genetically susceptible individuals.

Racial Factors also predispose patients to hyperglycemia and thus diabetes in:

1. Native Americans, Hispanics, Asian Americans, Pacific Islanders, or African Americans
2. History of gestational diabetes mellitus and polycystic ovarian syndrome.

CONCLUSION

The Prognosis of individuals with hyperglycemia depends on how well the levels of blood glucose are controlled. Chronic hyperglycemia can cause severe life- and limb-threatening complications. Changes in lifestyle, regular physical exercise, and changes in diet are the keys to a better prognosis. Individuals who maintain euglycemia have a markedly better prognosis and an improved quality of life compared to individuals who remain hyperglycemic. Once the complications of hyperglycemia have developed, they are irreversible. Countless studies have shown that untreated hyperglycemia shortens lifespan and worsens the quality of life. Thus, an aggressive lowering of hyperglycemia must be initiated, and patients must be closely followed. Studies suggest that one should try to achieve an HbA1C level of less than 7%. However, controlling blood sugars too tightly can result in hypoglycemia which is not well tolerated by elderly individuals who already may have a pre-existing cardiovascular disease. Patients must be educated that making changes in their lifestyle can markedly improve their prognosis. Some patients are prone to have greater glycemic variability of their blood sugars within a day and also variability for the same time on different days, thereby causing frequent episodes of hypoglycemia and hyperglycemia. These patients need close monitoring by an endocrinologist with a treatment plan intended to reduce the risks or at least maintain one risk while reducing the others.

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Section 04

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Dietary & Lifestyle Changes with Diabetes

Chapter 10

Nutritional Recommendations and Understanding of Medical Nutrition Therapy

Bipul Chandra Kalita

INTRODUCTION

Dietary guidelines play a pivotal role in guiding individuals towards selecting appropriate foods in adequate quantities across a range of food groups and achieving dietary diversity; thereby facilitating optimal nutrition throughout the lifecycle. These guidelines can also help in addressing the escalating incidence of under-/malnutrition, overweight/obesity and the non-communicable diseases like type-2 diabetes, hypertension, coronary artery disease and cancers in India. A significant proportion of premature deaths can also be averted by adopting a healthy lifestyle. It is well established that optimum nutrition plays an important role right from conception/fetal-stage till old age. Balanced diets not only ensure optimal growth/development but also minimize the risk of diet related non- communicable diseases (DR-NCDs) occurring in later life.

Nutritional recommendations from various agencies are:

1. A healthy mind needs a healthy body and healthy body needs mostly adequate amount of nutrients (Balanced diet) & exercise.
2. Foods are available in 10 different categories, out of which 5-7 food groups are to be consumed daily for a balanced diet.
3. Eat plenty of vegetables (particularly GLVs)/ fruits (in moderation) 400gm (five portion), excluding potatoes, sweet potatoes, casava and other starchy foods.
4. 25-30 grams of naturally occurring dietary fibres per day in adults.
5. Obtain good quality proteins (legumes & beans) and essential amino acids (EAAs) through appropriate combination of foods.
6. Use a variety of oils/fats in moderation; choose a variety of oil seeds, nuts, millets (nutri-cereals/shree-anna) and pulses/legumes to meet the daily needs of fats and esp. the essential fatty acids (EFAs).
7. Minimize the consumption of high fat and ultra processed foods (UPFs).
8. Unsaturated fats are preferable (found in fish, avocado, nuts, sunflower, soybean, canola & olive oil) to saturated fats (fatty meat, butter, palm, coconut oil, cream, cheese, ghee & lard).
9. Saturated fats should be less than 10% of total energy intake and trans-fat to be less than 1% of total energy intake (found in baked & fried foods, prepackaged snacks & food (e.g., frozen pizza, pies, cookies, biscuits, wafers, cooking oils & spreads).
10. Less than 10% of total energy intake from free sugar (equivalent 50 gm) should be in the diet. <5% of free sugar would be additional health benefit.
11. Drink adequate quantities of water (at least 5-

8 glass per day) and other fluids/beverages.

12. Restrict salt intake to the minimum (e.g., 5gm or less iodized salt per day).
13. Adopt appropriate pre-cooking/cooking methods to minimize the nutrient losses.
14. Ensure provision of extra food and appropriate healthcare during pregnancy & lactation.
15. Ensure exclusive breastfeeding for the first six months and continued breastfeeding till two years & beyond.

disease/sickness.

18. Include nutrient-rich foods in the diets of the elderly for better health and well being.
19. Be physically active and exercise regularly to maintain good health.
20. Adopt a healthy lifestyle to prevent overweight/obesity (esp. abdominal obesity), type 2 diabetes (T2D), hypertension (HTN), coronary artery disease (CAD) etc.

A balanced diet should provide not more than 45% calories from cereals & millets & up to 14% calories

FOOD GROUPS - Adequate quantities of foods from at least 5-7 food groups should be consumed on a daily basis.

1	Cereals and millets	Rice, wheat, millets and other cereals, etc.	
2	Pulses	Lentil, green gram, chickpea, rajma, cowpea, etc.	
3	Vegetables	Seasonal vegetables	
4	Nuts, oil seeds, oils and fats	Peanuts, walnuts, almonds, pistachio, hazel nuts, and other nuts, vegetable oils, etc.	
5	Green leafy vegetables (GLV)	Seasonal GLVs	
6	Fruits	Seasonal fruits	
7	Dairy	Milk, curd and butter milk	
8	Roots and tubers	Beetroot, radish, carrot, tapioca, sweet potato, etc.	
9	Flesh foods	Marine fish, poultry and lean cut meat	
10	Spices and herbs	Turmeric (haldi), ginger, mustard, pepper, cumin, corriander (dhania), etc.	

16. Start feeding home-made semi-solid complementary foods to the infant soon after the age of six months.
17. Ensure adequate quantities of nutritionally appropriate diets for children and adolescents, both in health and

from pulses, beans & meat. Rest of the calories should come from nuts, vegetables, fruits & milk, vitamins, minerals, phytonutrients, fibers. Bioactive substances, spices are also included in balanced diet.

In short - Calories should come from different sources are: **Carbohydrate 50 – 55%, Protein 10**

MY PLATE FOR THE DAY FOR 2000 Kcal

FOOD PYRAMID FOR BALANCED DIET for 2000Kcal

– 15 %, Dietary fats 20 – 30%.

MEDICAL NUTRITION THERAPY (MNT) a nutrition based (evidence based) treatment approach for managing health conditions through personalized nutritional plans developed by a specialist, registered dietitian, Registered Dietitian Nutritionist (RDN) for the patients overall health & wellness.

Goals: Primary goals of MNT are –

1. Promote optimum nutrition & health.
2. Prevent or manage chronic diseases.
3. Support medical treatment & therapy.
4. Improve quality of life.

MNT can help manage many different medical conditions. Some of them are – Diabetes mellitus, CKD, COPD, IBD, IBS, Cardiac disease, dyslipidemia, high BP, malnutrition including cancer, overweight & obesity, etc.

MEDICAL NUTRITION THERAPY IN DIABETES MELLITUS

Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications. Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications.

Goals and Principles of Medical Nutrition Therapy in Diabetes

The primary goals of MNT in diabetes are to:

1. Achieve and maintain individualized glycemic targets (e.g. HbA1c)

2. Manage body weight (especially in type 2 diabetes)

3. Optimize blood pressure and lipid profiles

4. Delay or prevent microvascular and macrovascular complications

5. Address individual preferences, cultural practices, food access, and quality of life

6. Support continued self-management and dietary flexibility.

Creating a Diabetes-Friendly Meal Plan

Diet plan for individuals with diabetes in India should include a balanced macronutrient composition: 50–55% carbohydrates, 10–15% proteins, and 20–30% fats. Focus should be on complex carbs, fiber-rich foods, lean proteins, and

healthy fats. Added sugars, refined carbs, and unhealthy fats should be limited in the diet. Portion control and regular physical activity should be included in the plan.

Tips for Adapting Traditional Indian Recipes

Indian diet chart for diabetes should have whole grains, lentils, and beans, and opt for steaming, boiling, grilling, or sautéing with minimal oil. Increase vegetable portions and practice portion control with smaller plates, encouraging mindful eating.

Indian diet chart for individuals with diabetes should include nutritious snacks like roasted chickpeas and yogurt with fruits, and replace sugary drinks with water or herbal teas.

Meal Patterns and Frequency

Flexibility in meal frequency and pattern is supported, provided total energy and macronutrient goals are met.

Some individuals and studies explore intermittent fasting, time-restricted eating, or meal-skipping strategies, but evidence in diabetes is still evolving or meal-skipping strategies, but evidence in diabetes is still evolving.

Behavioral Support

- Goal setting and self-monitoring (food diaries, SMBG)
- Motivational interviewing and problem-solving
- Gradual changes rather than radical overhauls
- Family involvement in meal planning
- Use of culturally adapted educational materials

CONCLUSION

Nutritional needs can be vary based on age, sex, activity level and medical conditions. A balanced diet for an individual is very much important for maintaining good health as well as preventing chronic illness.

Successful MNT requires not just prescriptions, but education, behavioral support, monitoring, and adaptation over time. In India, overcoming resource constraints, cultural patterns, and misconceptions is vital for effective implementation. Future research, especially in locally relevant settings, and the use of digital and tele nutrition platforms, may further strengthen the impact of MNT in diabetes care.

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Chapter 11

Carbohydrate Counting: A Scientific Approach to Optimizing Glycemic Control in Diabetes Mellitus

Purabi Dutta

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both. Carbohydrate counting has become a scientifically validated method to align insulin administration with dietary intake, particularly in individuals following intensive insulin therapy regimens. Carbohydrate counting (CC) is a pivotal strategy in medical nutrition therapy for diabetes mellitus (DM), facilitating precise regulation of postprandial glycaemia through quantitative assessment of carbohydrate intake and corresponding insulin adjustments.

PHYSIOLOGICAL BASIS

In healthy individuals, endogenous insulin secretion rises in direct proportion to carbohydrate intake. The insulin-to-carbohydrate ratio (ICR) quantifies this relationship and represents the number of grams of carbohydrate covered by one unit of rapid-acting insulin. The commonly used "500 rule" provides an approximate estimation: ICR = 500/Total Daily Insulin Dose (TDD. For example, a person with a total daily insulin dose of 50 units would have an ICR of 10, meaning 1 unit of insulin covers approximately 10 g of carbohydrate.

METHODOLOGY OF CARBOHYDRATE COUNTING

Carbohydrate counting is stratified into three progressive levels:LevelDescriptionApplicationLevel 1: Basic CCFocuses on recognizing carbohydrate-containing foods and maintaining consistent carbohydrate intake at meals.Suitable for individuals on fixed insulin doses or oral medications.Level 2: Intermediate CCInvolves estimating total grams of carbohydrates per meal using food labels, measuring tools, or standard exchange lists.Enables moderate flexibility with improved glycemic control.Level 3: Advanced CCIntegrates carbohydrate estimation with insulin-to-carbohydrate ratios (ICR) and correction factors for dynamic insulin dosing.Recommended for those on intensive insulin therapy and continuous glucose monitoring (CGM).

PRACTICAL CALCULATION EXAMPLES

Example 1: Estimating Carbohydrate Content

Using food composition tables or nutrition labels, an individual identifies the carbohydrate content of each food item in a meal:**Food ItemPortion SizeCarbohydrate (g)**2 slices whole wheat bread60 g30 g1 medium apple100 g15 g1 cup milk (250 ml)—12 gTotal—57 gThus, the total carbohydrate content of this meal is 57 g.

Example 2: Insulin Dose Calculation

If the individual's ICR = 1:10, this means one unit of insulin covers 10 g of carbohydrate.

Therefore, for a 57 g carbohydrate meal:

57g/10g per unit = 5.7 units of insulin

Rounded to 6 units of rapid-acting insulin before the meal.

If pre-meal blood glucose exceeds the target (e.g., 180 mg/dL), a correction factor or insulin sensitivity factor (ISF) is added, typically estimated by the "1800 rule":

ISF = 1800/TDD

For the same patient (TDD = 50 U):

ISF = 1800 ÷ 50 = 36 mg/dL per unit.

If the glucose target is 120 mg/dL and current reading is 180 mg/dL:

Difference = 60 mg/dL → 1.6 U correction insulin.

Thus, Total pre-meal insulin = 6 U + 1.5 U ≈ 7.5 U.

Example 3: Applying to Traditional Indian Foods

For a culturally adapted diet, carbohydrate values are derived from standard regional food databases:**Food ItemPortionCarbohydrate (g)**1 medium chapati (30 g wheat flour)115 g1 cup cooked rice (150 g)145 g½ cup dal (100 g)115 g1 small banana120 gTotal—95 gWith an ICR of 1:12 →

95 ÷ 12 = 7.9 U ≈ 8 U insulin before meal.

These examples illustrate how CC enhances precision and flexibility in real-world dietary planning across cultural contexts.

CLINICAL EVIDENCE

Numerous studies validate the clinical utility of carbohydrate counting. The DAFNE (Dose Adjustment for Normal Eating) trial demonstrated significant HbA1c reduction (mean −0.5%) and improved quality of life in adults with type 1 diabetes trained in CC (DAFNE Study Group, 2002). Further meta-analyses corroborate reductions in glycaemic variability, hypoglycaemic episodes, and overall improvement in metabolic parameters (Bell et al., 2018; Smart et al., 2020).

Continuous glucose monitoring (CGM) and hybrid closed-loop systems integrate CC algorithms to optimize automated insulin delivery and improve time-in-range (Bergenstal et al., 2018).

IMPLEMENTATION AND CHALLENGES

Successful execution of carbohydrate counting requires structured education by trained dietitians and diabetes educators. Skills in portion estimation, label reading, and digital tracking tools (apps, bolus calculators) are essential. Barriers include variable literacy, food labelling inconsistencies, and limited access to structured education programs in low-resource settings. Cognitive overload and estimation errors may also limit accuracy.

CONCLUSION

Carbohydrate counting is an evidence-based, physiologically grounded approach that enhances glycaemic precision and patient empowerment in diabetes management. When integrated with structured education, technological support, and cultural adaptation, it remains a cornerstone of modern diabetes care. Continued innovation in digital health tools will further refine and simplify its application in both clinical and community settings.

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Chapter 12

Role of Physical Activity and Exercise Recommendations in Diabetes Mellitus

N K Singh

INTRODUCTION

Diabetes mellitus (DM), which includes both type 1 diabetes (T1D) and type 2 diabetes (T2D), has become a global health crisis. More than 500 million adults are affected today, and this number is expected to cross 700 million by 2045. Physical activity (PA) and structured exercise are now considered as central parts of diabetes care. Their benefits extend far beyond lowering blood sugar—they improve heart health, body weight, bone and muscle strength, and mental well-being. The American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) both suggest at least 150 minutes of moderate aerobic activity each week, plus regular resistance training. For safe and effective practice, exercises need to be tailored to each individual, keeping in mind complications, blood sugar fluctuations, and practical barriers to regular activity.

HOW PHYSICAL ACTIVITY WORKS IN DIABETES

Immediate (Acute) Effects

Every bout of exercise activates important processes in the body:

- When muscles contract, they increase glucose uptake directly through **GLUT4 transporters**, even without insulin. For people with T2D, this bypasses insulin resistance and lowers blood sugar after meals. In T1D, this same pathway increases glucose use, but it may cause **hypoglycemia** during prolonged activity if insulin doses are not adjusted.
- Exercise also reduces the liver's glucose production and improves glycogen storage in muscle, adding to its glucose-lowering effect.

Long-Term (Chronic) Effects

Regular activity creates deeper adaptations that improve the underlying problems of diabetes:

- In T2D, exercise improves mitochondrial function and oxidative metabolism, which boosts insulin sensitivity by 20–30%.
- Resistance training increases muscle mass, which raises basal metabolism and improves glucose disposal.
- In T1D, exercise helps preserve whatever β-cell function is left and improves heart autonomic function. But because glucose swings are common, continuous glucose monitoring (CGM) is strongly recommended.

Systemic Benefits

The effects of exercise go far beyond sugar control. Exercise improves **blood vessel health**, reduces arterial stiffness, and lowers blood pressure. A 2023 *American Journal of Medicine Open* study showed that 150 minutes/week of moderate activity reduces systolic blood pressure by 4–6 mmHg and raises HDL cholesterol by 3–5 mg/dL. A 2025 *Lancet*

Public Health meta-analysis confirmed that this translates to a 15–20% reduction in cardiovascular events.

BENEFITS OF PHYSICAL ACTIVITY IN DIABETES

Glycemic Control

- Exercise is one of the most effective non-drug therapies to lower blood glucose.
- In T2D, a 2024 Journal of Diabetes and Metabolic Disorders meta-analysis found that aerobic + resistance training lowers HbA1c by 0.7–1.0%. Aerobic exercise alone reduces it by about 0.4%. In T1D, exercise stabilizes blood sugar swings, but CGM is necessary to prevent hypoglycemia.

Heart and Metabolic Health

- Diabetes increases cardiovascular risk 4–5 times, but regular activity offsets much of this risk.
- The 2023 ACSM consensus reported that 500 MET-min/week (about 150 min moderate

Table 1: Exercise Recommendations in Diabetes Mellitus

Component	Frequency	Intensity & Duration	Special Notes
Aerobic Exercise	3–5 days/week (not >2 days in a row off)	Moderate (50–70% HRmax) → 150 min/week OR Vigorous → 75 min/week	Break into ≥10-min bouts; monitor HR or RPE (12–14/20)
Resistance Training	2–3 non-consecutive days/week	Moderate (8–12 reps × 2–3 sets, major muscle groups)	Use free weights, machines, or body weight; progress gradually
Flexibility / Balance	2–3 days/week	Stretch 10–30 sec × 2–4 reps per muscle; add balance exercises	Yoga, Tai Chi; vital for older adults & neuropathy cases
Type 1 Diabetes	Same as above	Pre-exercise glucose: 100–180 mg/dL	Adjust insulin (↓ basal by 20–50%); add 15–30 g carbs/hr in long activity; avoid if glucose >250 mg/dL w/ ketones
Type 2 Diabetes	Same as above	Combined aerobic + resistance most effective	HIIT (20–30 min, 3×/week) works for busy patients; supervised start advised
Older Adults	Same as above	Low intensity (40–50% HRmax)	Emphasize balance/fall prevention; chair-based exercise if needed
Gestational Diabetes	Daily (20–30 min/day)	Moderate (walking, prenatal yoga)	Avoid high-impact activities; focus on safe mobility

aerobic activity) lowers all-cause mortality by 20% and cardiovascular events by 15%. Lipid benefits include a 10–20% drop in triglycerides and 3–5 mg/dL rise in HDL (Frontiers in Endocrinology, 2024).

Weight and Musculoskeletal Health

- Obesity, the main driver of T2D, is managed effectively through exercise.
- A 2025 *Lancet Public Health* study showed that 8,000–10,000 daily steps result in 2–5 kg fat loss over 12 weeks in people with T2D. Resistance training maintains lean mass and improves bone density, cutting fracture risk by 10–15%.

Mental Health and Quality of Life

- People with diabetes are twice as likely to suffer from depression and anxiety.
- Exercise improves mood through endorphin release and neurogenesis.
- A 2025 *Journal of Affective Disorders* meta-analysis showed that 150 minutes of moderate exercise weekly reduces depression scores by 15% and diabetes distress by 25%.

EXERCISE RECOMMENDATIONS IN DIABETES

Both ADA (2025) and ACSM (2023) have detailed guidelines which combine aerobic, resistance, and flexibility training, and tailor it to each individual.

- **Aerobic exercise:** 150 minutes/week of moderate intensity (brisk walking, cycling) spread over 3–5 days. Avoid more than 2 consecutive inactive days.
- **Resistance training:** 2–3 times/week on non-consecutive days, covering all major muscle groups. Start moderate (8–12 reps per set) and progress over time.
- **Flexibility and balance:** 2–3 times/week, including yoga or tai chi. Balance training is especially important for those with neuropathy.

WHY COMBINATION OF AEROBIC AND RESISTANCE EXERCISE?

Aerobic and resistance exercise acutely enhance insulin sensitivity by about 20%. With regular training regimens, insulin sensitivity can increase by more than 40%, and HbA1c improves by about 0.4–0.5%, which equals a fall of roughly 7–9 mg/dL in average blood glucose. When aerobic and resistance training are combined, insulin sensitivity can improve by nearly 70%, and HbA1c can fall by about 0.9%, translating to around 16 mg/dL lower average blood glucose. These changes are greater than those seen with either aerobic or resistance exercise alone. The improvement in insulin sensitivity also depends on exercise intensity. At moderate intensity (about 50% of VO_2 max), insulin sensitivity improves by around 50%. At higher intensity (around 80% of VO_2 max), it improves by nearly 80%.

Special Populations

- **T1D**: Maintain pre-exercise glucose between 100–180 mg/dL. For long sessions, consume 15–30 g carbohydrates per hour and adjust insulin (reduce basal insulin by 20–50%). Avoid exercise if glucose >250 mg/dL with ketones or <70 mg/dL.
- **T2D**: Combined aerobic + resistance training is most effective. High-intensity interval training (HIIT) is useful for busy individuals but should be supervised.
- **Older adults**: Use lower intensities (40–50% max HR). Prioritize balance and mobility. Chair-based exercises are suitable for those with limitations.
- **Gestational diabetes**: 20–30 min/day of moderate exercise (walking, prenatal yoga) is recommended, but high-impact activities should be avoided.

SAFETY CONSIDERATIONS ARE DEPICTED BELOW:

OVERCOMING BARRIERS

Despite clear benefits, only 30–40% of people with diabetes achieve ADA's exercise targets. Barriers include lack of motivation, time, fear of hypoglycemia, and physical limitations. Helpful strategies include:

- **Behavioral support**: Motivational interviewing, setting goals, and personalized counselling. A 2025 Diabetes Research and Clinical Practice RCT showed significant improvements in adherence.
- **Technology**: Wearables and apps improve accountability. A 2023 Journal of Medical Internet Research study found 20% higher adherence with digital tools.
- **Community programs**: Group exercise sessions increase social support, especially for older adults.

CONCLUSION

Physical activity is a cornerstone therapy for diabetes mellitus. It improves sugar control, heart health, weight, mental well-being, and life expectancy. The mechanisms involve both insulin-independent glucose uptake and long-term metabolic improvements. Following ADA and ACSM guidelines—150 minutes of aerobic exercise plus 2–3 sessions of resistance training weekly—provides the best outcomes. Programs should be personalized, safe, and adapted to patient needs. The future lies in overcoming barriers through technology, community support, and individualized care. With diabetes numbers rising worldwide, exercise remains one of the most effective, low-cost, and sustainable interventions available.

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Chapter 13

Supporting Right Approach to Health Behaviour with Alcohol and Smoking in Diabetes Mellitus

Anyam Borpuzari
Ripun Borpuzari

INTRODUCTION

Smoking and alcohol use in Diabetes Mellitus are linked with adverse effects on health. Physicians should educate their patients about the ill effects of these habits on their specific medical condition and advice against practicing them. When this advice is delivered in clear, personalized, and non-judgmental manner, patients can be motivated to stop these habits. The physician may then assist the motivated patient to quit/reduce these habits and prevent relapses through behavioural and pharmacological interventions. Non-doctor Health Care staff and Self-Help Groups can also be vital in motivating quitting and abstinence.

EFFECTS OF SMOKING AND ALCOHOL USE IN DIABETES

Smoking is bad for health. Everybody knows and accepts this. But what about the specific effects of smoking in an Individual with Diabetes Mellitus? ADA recognizes smoking as a factor contributing to macrovascular complications and cardiovascular ill health. Multiple studies have found a higher risk of morbidity and premature mortality in Diabetes amongst smokers as compared to non-smokers. Studies in animal models have also shown smoking (both traditional smoking and E-Cigarettes) to decrease insulin sensitivity. Compared to non-smokers, smokers have higher insulin requirement and serum triglyceride levels. An analysis of available literature by Sliwinska-Mosson M, et al in 2017 shows smoking cessation has a beneficial role in glycaemic control and limiting microvascular diseases, in addition to prevention of macrovascular complications.

When it comes to alcohol, on one hand Ethanol impairs gluconeogenesis in Liver, leading to fall in glucose production. Alcohol consumption increases the risk of Hypoglycaemia, especially in patients already on hypoglycaemic drugs. Dangerous hypoglycaemia may be ignored since symptoms of low blood sugar are often similar to symptoms of drunkenness. On the other hand, heavy consumption of alcohol can lead to higher blood glucose and A1C levels. Impairment of Gluconeogenesis is also associated with increased lactate production and decreased oxidation of fatty acids in the liver, which may lead to liver injury. Chronic heavy drinkers have a higher LDL level, have a six-fold increased risk of coronary artery diseases. Smokers are also at a higher risk of developing dyslipidaemia and cardiovascular complications- both as an independent risk factor, and via multiplicative interactions with other cardiac risk factors. These risks are further increased in patients of Type 2 Diabetes Mellitus, since small dense LDL particles present in such patients are more atherogenic.

RESPONSIBILITIES OF PHYSICIAN

Smokers who are given any sort of advice or recommendation by their physicians to stop smoking are 1.6 times more likely to attempt quitting. But

while over one in seven smokers see a physician each year, only 20% are given any advice or assistance in smoking cessation. Lack of detection of clinical clues of alcohol misuse by physicians also plays a role in its underdiagnosis and undertreatment. Screening of patients for alcoholism and providing brief interventions can lead to a 10-30% reduction in long term alcohol use and thereby reduce complications.

PLAN FOR SMOKING CESSATION

Every adult and adolescent diabetic patient should be asked about their smoking status. Non-smokers should be advised not to initiate smoking. Among smokers, cessation counselling should be a part of routine diabetes care. However, said advise should be tailored to patient's level of readiness to change. Physicians should not show negative judgement to patients who fail to or are unmotivated to quit. Counselling should be repeated at every clinical visit. Advice given during an intercurrent illness, hospitalization or before a medical procedure is more likely to motivate a quit attempt. Brief or structured behavioural interventions, advising increased physical activity have not been proven efficacious in promoting prolonged abstinence from smoking in Diabetics. Therapeutic education, providing knowledge to the patients about the problems associated with smoking in diabetes and benefits of cessation is associated with higher abstinence rates.

Motivational Interviewing can also be done to support smoking cessation. This has shown to have mixed results in different studies and different groups. One randomized control trial carried out in Kerela by KR Thankappan et al, India however shows promising results when Motivational Interviewing was conducted among diabetic patients. The study incorporated the US Dept of Health and Human Services 5 'A's and 5 'R' (see below) model of Motivational interviewing. The study showed that even brief interactions with a doctor was associated with a quit rate of 10-13%. If this was further supported by counselling sessions with trained non-doctor Health Care Worker, there was a 52% quit rate seen in 6 months follow up, and reduction of smoking levels to more than 50% of baseline in at least one in four non-quitters.

Drugs (Nicotine replacement therapy, Varenicline, Bupropion) may be offered to smokers to help in cessation of smoking unless contraindicated. All pharmacological interventions are more effective compared to placebos, and Varenicline is the most effective amongst them. Choice and dosage of drug should be individualized based on pregnancy status (nicotine, bupropion crosses the placenta), kidney function (Varenicline is renally excreted), mental health (Varenicline is associated with mood disorders), predisposition to seizures (Bupropion increases risk of seizures), etc.

FIVE 'A'S AND 'R'S MODEL OF MOTIVATIONAL INTERVIEWING ON CESSATION OF SMOKING

1. **ASK** the patient whether they use Tobacco at every clinical visit.
2. **ADVISE** every tobacco user to quit using messaging personalized to the patient's condition.
3. **ASSESS** every tobacco user's willingness to make a quit attempt.
4. **ASSIST** motivated patients to quit by giving behavioural advice and recommending pharmacological intervention.
5. **ARRANGE** for follow up visits in week 1, month one and then as needed.

If the patient remains unmotivated, counselling should be done to increase motivation. Discuss the 5 'R's. This increases the chances of future quit attempts in an unmotivated patient.

1. **RELEVANCE**- Encourage to indicate why quitting is relevant in their situation.
2. **RISKS**- Ask and help the patient identify potential negative consequences to continuing smoking.

3. **REWARDS**- Ask and help the patient identify potential benefits of stopping tobacco use.
4. **ROADBLOCKS-** Ask the patient to identify barriers to quitting, including factors that may have resulted in previous unsuccessful quit attempts. Provide treatment and advice to address them.
5. **REPETITION-** Repeat Motivational interviewing every time an unmotivated patient visits the clinic setting.

PLAN FOR ALCOHOL CESSATION

Alcohol has a complicated relationship with Blood Glucose levels. Acute intoxication is associated with hypoglycaemia, while chronic drinking can also lead to higher blood glucose levels and A1C. Excess alcohol use also has detrimental effects on various organ systems, which may add on to the complications of Diabetes Mellitus. Alcohol use in Diabetics can also indirectly cause problems because of abnormal eating habits and missed medications due to intoxication. Identification and management of Alcohol use disorders can therefore be helpful in Diabetes Mellitus. Use of Screening tools like the AUDIT questionnaire can help identify Alcohol Use disorders. Brief interventions in a clinical setting can help motivate the patient to avoid or control alcohol use. It is important to remind the patient that only they can decide to stop the negative impacts on their health associated with heavy drinking. When the patient considers changing their habits, a physician may suggest approaches to stop drinking. This may include advice like behavioural modifications, avoiding bars and other situations which may lead to heavy drinking.

When a patient agrees to stop drinking, a physician should consider and counsel the patient about the risks of alcohol withdrawal syndrome, withdrawal seizures, and Delirium Tremens. Long-acting benzodiazepines like Chlordiazepoxide may be needed to prevent/manage serious symptoms. Once the patient stops drinking, relapse prevention education can be given to the patients to identify situations which may lead to a return to drinking. Patients must be advised to avoid bars and other places where they might start drinking again. And if such a situation or relapse occurs, they must develop a coping mechanism to deal with it and prevent a relapse. All patients should be advised to try self-help groups like Alcoholics Anonymous. Drugs like Naltrexone, Acamprosate have modest beneficial effect on preventing relapse. Drugs that cause unpleasant effects like Disulfiram have a narrow risk-benefit ratio and are best given under supervision by someone.

CONCLUSION

ADA already recognizes alcohol as a factor that increases blood glucose and A1C levels. Smoking is also recognized as a risk factor in increasing complications of diabetes mellitus. In addition, there is ample evidence to suggest that smoking also negatively impacts glycaemic control. Both alcohol and smoking increases risk of cardiovascular complications in Diabetes Mellitus. Most Diabetics, in absence of other complications, do not get advice against smoking from Health Care Workers. This is a major missed opportunity to reduce the harmful effects of smoking on public health. Advice during intercurrent illness or before an upcoming therapeutic or diagnostic procedure is more likely to motivate smokers to quit. All Diabetic Patients should be counselled for Smoking Cessation in a clear, strong, and personalized manner. Effective behavioural interventions for cessation of smoking in diabetics include Therapeutic Education, Motivational Interviewing (5 'A's and 5 'R's model for Motivated and unmotivated patients respectively) and Pharmacological assistance. All diabetics should be counselled for smoking intervention on at every clinical visit.

The interplay between Alcohol use and Diabetes Mellitus is complicated. Advice regarding Alcohol

use in Diabetics should be personalized. Alcohol use disorder must be identified and treated, with consideration to the risk of Alcohol withdrawal Syndrome.

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Section 05

Section Editor : **Rupam Das**

Therapeutics and Guidelines

Chapter 14

A Critical Appraisal on Pharmacologic Approaches of Standards of Care in Diabetes - ADA 2025

Abhamoni Baro

INTRODUCTION

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" is developed and updated by the ADA's multidisciplinary Professional Practice Committee every year and published annually. These standards provide evidence-based guidelines on pharmacological and nonpharmacological treatment of diabetes mellitus in different ages, different settings, special groups and various diabetes associated complications. These guidelines are followed by clinicians and researchers worldwide. In this article, a critical appraisal of the recently published ADA Standard of care 2025 document on pharmacologic approaches to hyperglycaemia will be discussed, highlighting its strength and limitations.

STRENGTHS OF ADA 2025 STANDARDS OF MEDICAL CARE

1. CLARITY IN TREATMENT GOALS

ADA 2025 gives clearer treatment goals as compared to ADA 2024. There is much more clarity in approach to T2DM patient's therapeutics. The new guideline is more holistic, multifaceted, well-tailored to a person's metabolic and cardiovascular need. Person-specific factors which may affect choice of oral hypoglycaemic agents like the risk for hypoglycemia, risk factors for cardiovascular, renal, hepatic and other comorbidities have been addressed well by ADA 2025.

2. EMPHASIS ON DIABETES SELF MANAGEMENT

Diabetes mellitus (DM) is a chronic disease which needs life-long management. In absence of self-motivation, the goals of treatment cannot be achieved despite optimal drugs prescription. A healthy lifestyle behaviour, diabetes self-management education and support (DSMES) are a key to diabetes management. The latest ADA 2025 re-emphasizes that diabetes education is a priority in every person diagnosed with diabetes mellitus right from the beginning.

3. EARLY USE OF COMBINATION THERAPY

Type 2 diabetes (T2DM) is a progressive disease and requires multiple drugs with different mechanism of action to target the underlying multidimensional pathophysiology. Traditionally, the use of stepwise addition of medications was recommended but recently ADA guidelines support early initiation of combination therapy to achieve more rapidly the glycemic goals and for longer durability of the glycemic response. Combination therapy can be started with HbA1C levels 1.5–2.0% above individualized goal.

4. ADOPTION OF CARDIOMETABOLIC AND KIDNEY CENTRIC APPROACH RATHER THAN ONLY GLUCOCENTRIC APPROACH IN DRUG SELECTION

In those with T2DM and established or risk of ASCVD (atherosclerotic cardiovascular disease), an

SGLT2 inhibitor and/or GLP-1 RA with proven cardiovascular benefit is now being recommended by ADA 2025 which is independent of the baseline HbA1C or metformin use. The guideline also emphasizes on switching to these preferred medications even if glycemic control has been achieved with other oral hypoglycemic agents (OHAs) as this will reduce the risk of future ASCVD, HF, and/or CKD (chronic kidney disease). In those without risk factors, ADA 2025 says that shifting to SGLT2 inhibitors and GLP1RA will ensure metabolic and weight benefit as these molecules cause weight reduction.

In those with underlying CKD, selection of OHA will depend on both efficacy and safety as well as the potential to halt CKD progression. GLP-1 RAs and SGLT2 inhibitors have demonstrated renal benefits by reducing CKD progression and are now being recommended by ADA 2025 for managing T2DM with CKD. In presence of advanced CKD (eGFR <30 mL/min/1.73 m2), ADA 2025 recommends use of GLP-1 RA for glycemic control considering its lower risk of hypoglycemia along with cardiovascular event reduction. ADA 2025 clearly recognizes semaglutide as another first-line agent for people with CKD. In absence of dedicated kidney trials on liraglutide, dulaglutide, Tirzepatide (dual GIP and GLP-1 RA), these molecules are yet to get recognition for CKD. SGLT2 inhibitors like empagliflozin, canagliflozin, and dapagliflozin had shown beneficial effects on slowing CKD progression as well as improving CV outcomes and are highly recommended by the latest ADA now. Even in those with eGFR is <45 mL/min/1.73 m^2, SGLT2 inhibitors may have reduced glycemic efficacy but due to cardio-renal benefits and lower risk of hypoglycemia, they can be prescribed up-to an eGFR of 20 ml/min/1.73m^2 as per ADA 2025. The recommendation for metformin use in CKD remains same as in ADA 2024.

5. CLEAR RECOMMENDATION IN HEART FAILURE

ADA recommends SGLT2 inhibitors if there is heart failure (HF) with either reduced or preserved ejection fraction as this class of drug reduces HF hospitalizations irrespective of underlying HbA1C. In an adult with T2DM, obesity and symptomatic HF with preserved ejection fraction (HFpEF), ADA recommends a GLP-1 RA with evidence of both glycemic and HF benefit.

6. ADDITIONAL RECOMMENDATION FOR MASLD

Both T2DM and T1DM subjects with obesity are at high risk of developing MASLD (Metabolic Dysfunction Associated Steatotic Liver Disease) and MASH (Metabolic Dysfunction Associated Steatohepatitis) as well as MASH cirrhosis. Hence, ADA 2025 emphasizes on considering the presence of MASLD or MASH when choosing glucose lowering therapies. GLP-1 RA, and a dual GIP and GLP-1 RA have shown potential benefits in reducing hepatic steatosis in biopsy-proven MASH. ADA 2025 this year had started recommending combination therapy of pioglitazone with GLP-1 RA for treatment of hyperglycemia in adults with T2DM and biopsy proven MASH as well as in those with high risk of clinically significant hepatic fibrosis diagnosed by non-invasive tests.[1] Since insulins, sulfonylureas and thiazolidinediones promote weight gain, these drugs should be used judiciously at the lowest possible dose in those with obesity as per ADA. As of now, Tirzepatide and semaglutide have demonstrated highest efficacy in terms of glucose lowering and weight reduction, followed by other GLP1RAs (dulaglutide, liraglutide, exenatide). Other OHAs like metformin, DPP-4 inhibitors, alpha-glucosidase inhibitors, are weight neutral and ADA 2025 calls them add-on therapies in adults with T2DM with obesity. ADA do not recommend combining dipeptidyl peptidase-4 (DPP-4) inhibitors

with a GLP-1RA or a dual GIP and GLP-1 RA because no additional glycemic benefits are seen with addition of DPP4i.

7. AID SYSTEM AND INHALED INSULIN ARE ADDED IN MANAGEMENT OF T1DM

Automated insulin delivery (AID) systems should be offered to all adults with T1DM. For most adults with T1DM, ADA recommends insulin analogs or inhaled insulin over injectable human insulins in order to minimize hypoglycaemia risk. ADA states that early use of continuous glucose monitoring (CGM) for adults with T1DM improves glycemic control and quality of life.

8. COMBINATION OF INSULIN WITH GLP1RA OR DUAL AGONIST RECOMMENDED FOR GREATER A1C REDUCTION

ADA recommends initiating insulin in T2DM regardless of background anti-hyperglycemia drugs if symptoms of hyperglycemia are present or A1C >10% or blood glucose >300 mg/dL. Newer ADA states that in absence of insulin deficiency, a GLP-1 RA or a dual GIP and GLP-1 RA can be preferred over insulin. Otherwise, combination therapy of insulin with a GLP-1 RA or a dual agonist is recommended if greater glycemic effectiveness along with weight loss is targeted in adults with T2DM.

9. NEWER RECOMMENDATIONS REGARDING SPECIAL GROUPS PREGNANCY

ADA 2025 recommends preconception counselling be started right from puberty in all girls with diabetes. Now there is more clarification on the recommended eating pattern during pregnancy. The insulin recommendations are merged for both preexisting diabetes and GDM(Gestational diabetes mellitus). Insulin is the ideal treatment for T1DM, T2DM in pregnancy and GDM. Metformin and glyburide should not be first-line agents as per ADA 2025 due to passage through placenta. Metformin started to treat polycystic ovary syndrome and for ovulation induction, should be stopped by the end of first trimester. ADA 2025 recommends AID (automated insulin delivery) system with pregnancy-specific glucose goals to be used during pregnancy. For glycemic monitoring ADA 2025 considers CGM (continuous glucose monitoring) to be beneficial for both T1DM and T2DM in pregnancy. ADA now allows CGM in conjunction with blood glucose monitoring in pregnancy to achieve glycemic goals. A significant update has been made on statin use in pregnancy this year and ADA states that statin be considered in pregnancy with DM in high-risk cases such as prior history of ASCVD or familial hypercholesterolemia, when benefits outweigh risks. A HbA1c target of < 6% during pregnancy is stated in ADA 2025. Other recommendation includes starting low dose aspirin (100-150mg/day) at 12-16 weeks and preconception folic acid supplements (400–800 mg/day) and potassium iodide supplements (150mg/day). A blood pressure goal of 110-135/85mmHg is clearly stated.

CHILDREN AND ADOLESCENT

The latest ADA 2025 recommends AID systems should be offered to children with T1DM who are capable of using it safely. In place of AID systems insulin pump therapy can also be used. CGM should be offered to all at diagnosis or as soon as possible in children with T1DM on multiple insulin injections or insulin pump therapy. An A1C goal of <7% is recommended for most children and adolescents, a goal of <6.5% if no risk of significant hypoglycemia and a goal of <7.5% in those with hypoglycemia unawareness and lack of CGM. In children with T2DM, ADA 2025 recommends metformin as first line therapy along with lifestyle modifications if A1C is <8.5%. But if A1C is ≥8.5% or blood glucose ≥ 250 mg/dl without ketoacidosis, these children should be treated with long-acting insulin and metformin. If glucose goals are not met then GLP-1 RAs and/or

empagliflozin is recommended in youth with T2DM aged 10 years and above.

OLDER ADULTS

ADA 2025 recommendations for older adults include offering CGM to those with T2DM on insulin as well as to elderly with T1DM and offering AID technology to reduce hypoglycemia. The use of SGLT2 inhibitors in older adults was expanded and ADA have stated its benefit in elderly with established ASCVD and/or heart failure as well in CKD. ADA 2025 calls for de-intensifying hypoglycemia causing drugs (insulin, sulfonylurea or meglitinides) in elderly and switching to drugs with low hypoglycemic risk and proven cardiovascular benefit.

ALPELISIB INDUCED DM

Alpelisib, a PI3K inhibitor has been associated with diabetes mellitus in 60% cases which resolves upon treatment cessation. Metformin has been recommended to treat Alpelisib-induced hyperglycemia and prediabetes state. SGLT2 inhibitors and pioglitazone are second or third-line drugs.

LIMITATIONS OF ADA 2025 STANDARDS OF MEDICAL CARE: FROM A PERSONEL PERSPECTIVE

For physicians and researchers, ADA guidelines are very informative, useful and praiseworthy. However, a critical appraisal of this document showed certain issues that needs attention in future publications.

1. Need to define duration of use of costly medications like GLP1RA or dual agonists. These class of drugs often need continuation for a longer duration or life long treatment for long term benefit. If these drugs are stopped, it leads to rebound of obesity and loss of cardio-renal effects. ADA in its future publications should also discuss management in those who prefer to stop these medications due to intolerance or economic constraint.
2. Need to add a section on management of diabetes with sarcopenia or frailty, especially in older adults. Loss of lean muscle mass in diabetes leads to functional disability. Furthermore, OHAs which cause weight loss (GLP1-RA) may further aggravate loss of lean muscle mass along with fat mass in a sarcopenic adult and this issue should be addressed.
3. Since longevity have increased with more and more older adults are living beyond 75 years age, the ADA guideline should define extreme older age (eg: above 75 years) as a separate group considering their different needs, presence of multiple comorbidities, poor gastrointestinal tolerability, frailty and polypharmacy. This age group needs special consideration and glycemia treatment should not be generalized with that for all older adults.

CONCLUSION

ADA recommendations are annually revised considering the new evidences to improve diabetes care delivery and health outcomes. The latest ADA 2025 standard of care included detailed sections discussing approach to T2DM patients with CKD, CVD and metabolic abnormalities, giving a better stepwise approach. Newer drugs like GLP1RA, GIP/GLP1RA and SGLT2i for ASCVD and CKD are now being recommended by ADA 2025. Clinicians should take guidance from the recent ADA 2025 Standard of Medical Care and implement the changes in patient care.

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Chapter 15

Global Perspective: IDF 2025 Recommendations on Therapeutics

Debomallya Bhuyan
Aishwarya R Chandran

INTRODUCTION

The 2025 IDF Global Clinical Practice Recommendations address the escalating global burden of type 2 diabetes mellitus (T2DM), with projections showing alarming increases in prevalence, particularly in low- and middle-income countries. Diabetes mellitus has become a mounting health crisis worldwide. According to the International Diabetes Federation's 2025 Diabetes Atlas, roughly **589 million adults aged 20–79** globally are living with diabetes. Projections indicate this number will increase to **approximately 853 million** by 2050, representing nearly **1 in 8 adults**. The greatest increase in the prevalence has been observed in low- and middle-income countries where lifestyle transitions, urbanisation, aging populations, and expanding obesity have created fertile ground for disease rise. India carries a large fraction of this burden. In 2024, India had about **89.8 million** adults aged 20-79 with diabetes, with an age-standardised prevalence of **10.5%**. By 2050, this figure is projected to increase to approximately **156.7 million**. The problem is compounded by under diagnosis, an estimated **43%** of Indians with diabetes are unaware of their condition (~38.6 million people), highlighting large gaps in detection.

Beyond prevalence, the complications of diabetes such as cardiovascular disease, diabetic nephropathy, retinopathy, neuropathy, cognitive decline, liver disease, mood disorders, and increased susceptibility to infections impose substantial morbidity, mortality, and economic cost. Even before clinical diagnosis, many individuals already harbour microvascular or macrovascular damage. The guidelines emphasize early detection through risk-based screening, structured prevention strategies, and equitable access to care. Weight management remains central, with lifestyle interventions as the foundation, supplemented by pharmacotherapy and metabolic bariatric surgery where appropriate. Cardio-renal protection through integrated use of Sodium-Glucose Cotransporter-2 inhibitors (SGLT2 inhibitors), Glucagon-Like Peptide-1 (GLP-1) receptor agonists, and non-steroidal mineralocorticoid receptor antagonists (MRAs) is highlighted as a major therapeutic advance. Furthermore, the recommendations include updated strategies for managing metabolic dysfunction-associated steatotic liver disease (MASLD) in T2DM, advocating early identification and targeted interventions. Collectively, these guidelines provide a pragmatic, person-centred, and resource-sensitive framework for improving outcomes in people with diabetes.

WEIGHT CONTROL IN T2DM MANAGEMENT

Obesity is not only a major risk factor for the onset of type 2 diabetes but also plays a pivotal role in the development and progression of its complications, as it disrupts both insulin action and pancreatic function, making weight management an essential

component of both the prevention and treatment of T2DM.

Intensive Lifestyle Intervention (ILI)

- Focus: caloric restriction, balanced nutrition, increased physical activity, behavioural counselling.
- Look AHEAD trial: Sustained weight loss of around 6% showed significant benefits like improved nephropathy and neuropathy though CVD event were similar to control group.
- Very-Low-Calorie Diets (VLCD) inducerapid weight loss and showed high rates of remission (**DiRECT Trial of UK and DIADEM-1 Trial of Qatar)** but long-term maintenance can be challenging.
- Physical Activity: At least 150 minutes/week of moderate-intensity exercise, combined with resistance training, enhances weight loss and insulin sensitivity.

Incretin based Pharmacotherapy for Weight Management

- **GLP-1 Receptor Agonists - Liraglutide 3.0 mg, Semaglutide 2.4 mg:**
  - Reduce weight and HbA1c; improve cardiometabolic risk.
  - Semaglutide trials: 10–15% weight loss with notable diabetes remission rates.
- **Dual and Triple Agonists:**
  - Tirzepatide (GLP-1/GIP) and retatrutide (GLP-1/GIP/glucagon) show superior weight loss (up to 20%).

In many parts of the world where effective weight-loss medications are scarce or unaffordable, emphasis should be placed on nutrition education and the use of blood glucose–lowering drugs that have minimal adverse effects on weight. This includes drugs like Metformin (weight neutral, first-line), if available SGLT2 inhibitors (weight loss, cardio-renal benefit), dipeptidyl peptidase 4 (DPP4) inhibitors and α-glucosidase inhibitors (weight-neutral). Avoid weight-gaining drugs (sulfonylureas, glitazones) unless necessary.

Metabolic Bariatric Surgery (MBS)

- Indicated in people with BMI ≥30 kg/m² with uncontrolled diabetes; may be considered at lower BMI in Asian populations.
- Superior to lifestyle/pharmacotherapy for durable weight loss and diabetes remission.
  - ARMMS-T2D trial: 37.5% remission at 3 years post-surgery vs 2.6% with lifestyle/medical care.
- In the long run, it reduces microvascular and macrovascular complications, CVD, and mortality. However, surgical risks, cost and need for lifelong follow-up are few limiting factors of MBS.

CARDIO-RENAL PROTECTION IN TYPE 2 DIABETES

T2DMsubstantially raises the risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), chronic kidney disease (CKD), and premature death. A systematic review of over four million individuals with T2DM showed a cardiovascular disease (CVD) prevalence of 32%, with high rates of coronary artery disease, HF, angina, myocardial infarction, and stroke, and nearly half of all deaths attributed to CVD. HF is a major yet underappreciated complication, associated with high morbidity, mortality, and hospitalizations, though preventable and treatable. CKD affects about 40% of people with T2DM, with greater prevalence among younger patients and certain ethnic groups, highlighting the importance of early detection.

Pillars of Management To Improve Cardio Renal Outcomes In People With T2DM

1. Glycaemic Control

Early and intensive glucose management lowers risks of CVD, retinopathy, and nephropathy.

2. Risk Factor Control

Control of blood pressure, dyslipidaemia, smoking, obesity/overweight and other modifiable risk factors form a core element of diabetes and cardio-renal care, becoming all the more essential when advanced therapies are of limited availability.

(i) Blood Pressure

- If safely achievable, target a blood pressure<130/80 mmHg. Measure BP at every visit.
- First-line: ACE inhibitors (ACEi) or ARBs; particularly recommended with elevated UACR. Avoid combinations of ACEi and ARB and ACEi/ARBs with direct renin inhibitors.
- Incidence of CVD events significantly reduce with an intensive blood pressure control targeting an SBP <120 mmHg as opposed to the standard target SBP of less than 140 mmHg.

(ii) Lipids

- Assess lipids at diagnosis and annually.
- LDL targets: < 70 mg/dl for primary prevention; <55 mg/dL for secondary prevention.
- Statins are the first choice of therapy; alternatives are used if statin-intolerant or goals are unmet. KDIGO recommends statins in T2DM adults aged 18–49 years with CKD (not on dialysis or transplant).
- Address hypertriglyceridemia when needed.

3. Other Standard Therapies

(i) ACEi/ARB: Recommended in T2DM with CKD and albuminuria (A2 or A3), but combinations of ACEi and ARB and ACEi/ARBs with direct renin inhibitors are to be avoided.

(ii) Beta-blockers: Reduce mortality and HF hospitalisation in T2DM with HFrEF.

4. Blood Glucose-Lowering Therapies

(i) SGLT2 Inhibitors & GLP-1 Receptor Agonists

- Now central to managing cardio-renal risk in T2DM.

SGLT2 Inhibitors

- Provide consistent benefit in reducing HF hospitalisation, kidney disease progression, and adverse renal outcomes. Benefits extend to patients with or without diabetes, across HF phenotypes, and regardless of baseline kidney function.

GLP-1 Receptor Agonists

- Meta-analyses showed reductions in all-cause and CV mortality (~12–13%), stroke (fatal 26%, non-fatal 13%), kidney outcomes (~18–24%).
- Limited evidence in HF; STEP-HFpEF DM trial suggests symptom and functional improvement.
- FLOW trial (semaglutide) demonstrated renal and CVD benefit.
- Retinopathy risk noted in SUSTAIN-6 (under further study).

Combination Therapy: Real-world data suggest additive benefit (lower mortality, weight, BP, HbA1c), but trial evidence is lacking and certainty is low.

(ii) Tirzepatide

- Dual GIP/GLP-1 receptor agonist; induces significant weight loss.SUMMIT trial with tirzepatide (up to 15 mg subcutaneously once weekly) suggest improved HF outcomes; CVOT (SURPASS-CVOT) is ongoing.

Other Therapies

- Metformin: Long-term benefit in UKPDS (↓ MI, stroke, and mortality).

- Sulfonylureas: Neutral CV outcomes; higher hypoglycaemia risk.
- Alpha-glucosidase inhibitors: No CV benefit.
- Thiazolidinediones: Neutral to adverse CV outcomes; ↑ HF risk.
- DPP-4 inhibitors: CV neutral, but Saxagliptin ↑ HF hospitalisation.
- Insulin: No CV advantage in major trials.

5. Mineralocorticoid Receptor Antagonists (MRAs)

(a) Steroidal MRAs (spironolactone, eplerenone)

- Reduce death and heart failure (HF) hospitalisation
- Require caution with renal impairment or hyperkalaemia.

(b) Non-steroidal MRA (finerenone)

- Proven to reduce kidney failure, CV death, non-fatal MI/stroke, and HF hospitalisation in T2DM with CKD already on ACEi/ARB.
- Effective regardless of SGLT2 inhibitor use.
- Recent evidence shows benefit in HF with mildly reduced/preserved EF.

MANAGEMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN TYPE 2 DIABETES

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as NAFLD (Non-Alcoholic Fatty Liver Disease), is the most prevalent chronic liver disease globally and is strongly linked to type 2 diabetes, prediabetes, and obesity. The key focus is early identification of those at risk for advanced fibrosis, particularly those with **abdominal obesity** or **abnormal liver tests**. A two-step screening approach is recommended, starting with the **Fibrosis-4 index** (FIB-4) followed by **imaging** such as vibration-controlled transient elastography (VCTE)/Magnetic resonance elastography (MRE) if risk is moderate or high.

MASLD-specific interventions

I. Lifestyle modification and weight loss

Importance of dietary and lifestyle changes promoting weight loss cannot be emphasized enough. In overweight and obese MASLD people, weight loss of ≥5% reduces liver fat, 7–10% improves hepatic inflammation, and ≥10% improves fibrosis.

II. Pharmacotherapy

Resmetirom	First FDA-approved drug (2024) for non-cirrhotic MASH with moderate to advanced hepatic fibrosis. Liver-specific thyroid hormone β-1 receptor agonist; taken orally (80–100 mg daily, weight based).Significant resolution of MASH, fibrosis improvement, and LDL reduction compared with placebo were observed in a phase 3 RCT. Common side effects observed were diarrhoea, nausea, vomiting and pruritus. As of now there is no approved drug for MASH with cirrhosis.
Blood Glucose-Lowering Medications: No single diabetes drug is officially approved for MASLD, but some show benefits through weight loss or metabolic effects.	
Metformin	Safe, but no proven effect on steatohepatitis; to be continued even in cirrhosis unless contraindicated due to renal failure or hepatic decompensation.
Sulfonylureas	No MASLD benefit; higher hypoglycaemia risk in cirrhosis.
Insulin	Reduces steatosis via improved glycaemia, but may increase hepatic fat deposition; preferred in decompensated cirrhosis for glycemic control.
Pioglitazone	Improves MASH as found in various phase 2 RCTs (phase 3 trials have not been done yet) but limited by side effects and availability; effect on fibrosis unclear.
SGLT2 inhibitors	Reduce steatosis and liver enzymes (mainly via weight loss), no proven fibrosis effect; strong cardio-renal benefits
GLP-1 receptor agonists	Promote weight loss, improve steatosis, and some (notably semaglutide in phase 3 ESSENCE trial) improve fibrosis. Not effective in cirrhosis but linked to reduced progression and mortality in T2DM cohorts.
Statins	Safe for people with T2DM and MASLD, including compensated cirrhosis. Regular use lowers risk of new onset liver disease (15%) and liver-related deaths (28%). As there is limited evidence in decompensated cirrhosis, statins are to be used cautiously with monitoring.
Metabolic Bariatric Surgery (MBS)	Effective for MASLD/MASH in severe obesity, improving T2DM and heart health. MBS Can resolve MASLD/MASH, but advanced fibrosis may persist. In compensated cirrhosis MBS may be cautiously advocated while it is contraindicated in decompensated cirrhosis.

SGLT2 inhibitors and **GLP-1 receptor agonists** are preferred in T2DM with MASLD due to combined metabolic and cardio-renal benefits. Despite diagnostic and treatment limitations—especially in resource-constrained settings—early identification and targeted interventions in at-

risk individuals of T2DM with MASLD can prevent progression to cirrhosis and reduce associated cardio-renal complications.

CONCLUSION

The 2025 IDF recommendations reinforce the urgent need for comprehensive, person-centered diabetes care that prioritizes prevention, early detection, and multidisciplinary management. Lifestyle modification remains the cornerstone, but evidence-based pharmacological and surgical options provide additional means to achieve durable outcomes. With cardio-renal complications and MASLD emerging as critical concerns, tailored use of novel therapies can significantly reduce morbidity and mortality. Adaptability across diverse healthcare settings ensures these guidelines remain globally relevant, offering a practical roadmap to address the growing diabetes crisis.

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Chapter 16

An Updated Appraisal of RSSDI Clinical Guidance in Diabetes

Banshi Saboo
Subhajyoti Ghosh

INTRODUCTION

Guidelines development for diabetes must reconcile high-quality evidence with local realities. India carries a disproportionate burden of diabetes and its complications; therefore, guidance that is context-sensitive is essential. The Research Society for the Study of Diabetes in India (RSSDI) produces clinical practice recommendations and consensus statements intended for Indian physicians, diabetologists, and allied health professionals. Recent RSSDI documents (notably the 2022 Clinical Practice Recommendations and focused expert consensuses in 2024) address prevention, pharmacotherapy, monitoring, vaccinations, and comorbidity management. This appraisal evaluates the scope, evidence-basis, clarity, strengths, and limitations of RSSDI guidance published in the recent cycle (2019–2024), and provides priorities for future updates. Recommendations for future RSSDI guideline development—methodology, evidence synthesis, grading, and implementation research—are proposed.

METHODS OF APPRAISAL

This appraisal reviewed RSSDI documents publicly available on the RSSDI website and in peer-reviewed sources, including:

- RSSDI Clinical Practice Recommendations (2022). (rssdi.in)
- RSSDI Expert Consensus for Optimal Glucose Monitoring (2024). (rssdi.in)
- RSSDI update on vaccination in people with diabetes (2024). (rssdi.in)
- RSSDI guidelines on hypertension in people with diabetes (2022). (PubMed)
- Earlier RSSDI consensus documents on insulin therapy and other areas (2019). (rssdi.in)

Evaluation criteria included: scope and topical coverage; clarity and actionability of recommendations; strength and transparency of evidence grading; attention to resource-stratified care; alignment with international guidance (ADA, EASD, WHO) where relevant; and implementation feasibility in Indian practice. When available, publication dates and placement on the RSSDI site were recorded to evaluate currency.

KEY RECENT RSSDI RECOMMENDATIONS — SUMMARY

1. Comprehensive 2022 Clinical Practice Recommendations

The RSSDI 2022 Clinical Practice Recommendations provide broad coverage—from prevention and diagnosis to pharmacotherapy and complication screening—and include India-specific adaptations (e.g., thresholds and screening approaches for prediabetes and gestational diabetes). The 2022 document emphasizes lifestyle intervention, early intensification of therapy where

indicated, and context-adapted pharmacologic choices. (rssdi.in)

2. Glucose monitoring: 2024 expert consensus

In late 2024 RSSDI published an expert consensus focused on optimal glucose monitoring for India. The statement reviews self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM; intermittently scanned and real-time), HbA1c use, and challenges unique to LMIC settings—cost, device access, and patient literacy. It provides pragmatic recommendations on when to use CGM vs SMBG (for example, CGM for people on intensive insulin regimens, SMBG for many people on oral agents), and stresses standardized reporting and patient education. (rssdi.in)

3. Vaccination guidance update (2024)

RSSDI's 2024 vaccination update for people with diabetes reiterates the importance of influenza, pneumococcal, hepatitis B, and other context-appropriate vaccines, and aligns recommendations with CDC/ADA principles while factoring Indian epidemiology and vaccine availability. The document highlights age-based and risk-based vaccination indications and addresses vaccine formulations and schedules relevant to India. (rssdi.in)

4. Cardiovascular risk and hypertension guidance (2022)

RSSDI's 2022 guideline on hypertension in diabetes gives practical blood pressure targets, choice of antihypertensives (ACE inhibitors/ARBs as first-line in many cases), and emphasizes screening and integrated risk management for cardiovascular disease (CVD). The guidance is explicit about combining BP control with glycaemic and lipid management for risk reduction. (PubMed)

5. Insulin therapy and other consensus documents

RSSDI has maintained and updated practical consensus statements on insulin initiation, intensification, and combinations with newer agents (SGLT-2 inhibitors, DPP-4 inhibitors), recognizing resource and affordability constraints, and emphasizing hypoglycaemia avoidance strategies. (rssdi.in)

Scientific Method Framework for Appraisal

Criterion	Assessment
1. Research Question / Objective	Clearly defined — to update evidence-based, India-specific clinical practice recommendations for T2DM care addressing diagnosis, prevention, nutrition, pharmacologic management, complications, and comorbidities.
2.Hypothesis/ Rationale	Based on recognition that Western guidelines (ADA, EASD) require contextual adaptation to India's epidemiology, socioeconomics, and healthcare infrastructure.
3. Literature Review	Extensive literature review with multiple Indian and international studies cited; however, not always systematic or meta-analytically synthesized.

Criterion	Assessment
4. Study Design / Methodology	Expert consensus process using subgroup panels for each domain. Explicit methodology of evidence appraisal (e.g., GRADE scoring) not uniformly detailed; reliance largely on expert interpretation of available evidence.
5. Data Sources and Evidence Base	Draws on RCTs, cohort studies, meta-analyses, and landmark Indian trials (e.g., IDPP, D-CLIP). However, the grading of evidence (strong/moderate/weak) is not systematically presented across all sections.
6. Analysis and Synthesis	Each section integrates available evidence with practical recommendations categorized as *Recommended Care* vs *Limited Care*, reflecting tiered health-resource settings — a major strength for low- and middle-income applicability.
7. Results (Recommendations)	Covers 20+ thematic areas: Diagnosis, Prevention, Nutrition, Oral/Injectable therapy, Precision diabetology, Acute and chronic complications, Comorbidities, and Special populations. Provides thresholds, drug choices, and management algorithms.
8. Discussion and Interpretation	Balances global evidence with contextual adaptation (e.g., caution on HbA1c-only diagnosis due to hemoglobinopathies). Emphasizes preventive, lifestyle, and primordial interventions relevant to Indian epidemiology.
9. Limitations and Bias	Acknowledged limitations include lack of uniform HbA1c standardization and limited resource access. Potential bias from expert consensus without full disclosure of conflicts of interest or systematic GRADE use.
10. Conclusion / Implications	The guideline successfully provides India-specific, tiered, implementable recommendations for T2DM. Encourages integrated care and public health alignment.

STRENGTHS OF RSSDI GUIDANCE

1. India-centric scope and relevance

RSSDI consistently contextualizes international evidence to Indian patient profiles (younger age of onset, high cardiometabolic risk, socioeconomic diversity), which enhances clinical relevance compared to off-the-shelf international guidance.

2. Practical, actionable recommendations

Many RSSDI documents are pragmatic (for example, providing clear thresholds for initiating metformin in prediabetes or a resource-stratified approach to glucose monitoring), facilitating day-to-day decision making in primary and secondary care. (rssdi.in)

3. Focus on implementation challenges

Recent RSSDI statements explicitly discuss barriers—device affordability, patient literacy, access to specialists, and vaccination delivery in low-resource settings—which is essential for applicability.

4. Breadth of specialty topics

RSSDI has produced focused guidance across complications (retinopathy screening with VRSI collaboration), comorbidities (hypertension), and ancillary areas (vaccination), adding to the utility for multidisciplinary teams. (rssdi.in)

LIMITATIONS AND AREAS NEEDING IMPROVEMENT

1. Variable methodological transparency and grading of evidence

While some RSSDI documents summarize evidence, there is variability in transparent reporting of systematic search methods, inclusion/exclusion criteria, and formal evidence-to-recommendation grading (e.g., GRADE). Standardizing methods and reporting would improve credibility and usability for those who need to weigh strength of evidence.

2. Limited explicit cost-effectiveness modelling

Although the guidelines consider affordability qualitatively, formal health-economic analyses (cost-effectiveness or budget-impact) are infrequently presented. Given the resource limitations in many Indian settings, inclusion of pragmatic cost-effectiveness data would strengthen recommendations—particularly for technologies (CGM, novel agents) with high upfront costs. (rssdi.in)

3. Need for clearer prioritization and resource stratification

Some recommendations could benefit from clearer tiering (e.g., essential vs desirable vs optional interventions) for primary care, district hospitals, and tertiary centres. This would help non-specialists implement guidance more consistently.

4. Greater alignment and explicit comparison with international guidance

While RSSDI adapts international evidence, side-by-side comparisons (e.g., where RSSDI intentionally diverges from ADA/EASD recommendations and why) are not always explicit. Explicit rationales help clinicians understand departures and defensibly adapt practice.

5. Implementation and audit tools are limited

Guidelines would be more impactful if paired with practical implementation aids (flowcharts, EMR order sets, patient education modules, quality metrics) and suggested audit measures for tracking uptake and outcomes.

SPECIFIC CONTENT APPRAISALS & SUGGESTIONS

Glucose monitoring (2024 consensus)

Appraisal: The 2024 consensus suitably recognizes CGM's clinical value (hypoglycaemia detection, time-in-range metrics) while recommending SMBG where CGM is unaffordable or unavailable. The document provides practical indications and training needs for device use—important in low-literacy contexts. (rssdi.in)

Suggestion: Add tiered algorithms that specify minimum acceptable monitoring strategies per care level (e.g., primary care: SMBG and periodic HbA1c; secondary care: SMBG plus targeted

intermittent professional CGM; tertiary: rtCGM for complex insulin users). Include cost-utility estimates or procurement guidance to help health systems plan device roll-out.

Pharmacotherapy and early combination therapy

Appraisal: RSSDI's 2022 recommendations emphasize early intensification, use of metformin as first line where tolerated, and consideration of SGLT-2 inhibitors/DPP-4 inhibitors per comorbidity profile. Existing consensus documents discuss combination strategies. (rssdi.in)

Suggestion: Provide explicit algorithms for SGLT-2 and GLP-1 RA use stratified by CVD/CKD risk and cost considerations, and include renal-function thresholds and monitoring schedules aligned to Indian prescribing realities. When recommending newer agents, RSSDI should explicitly state monitoring for adverse effects and renal dose adjustments.

Vaccination

Appraisal: RSSDI's 2024 vaccination update aligns with international practice and tailors suggestions to the Indian context (age thresholds, vaccine formulations). This is timely and important for reducing infection-related morbidity. (rssdi.in)

Suggestion: Add implementation guidance for opportunistic vaccination at diabetes clinics and primary care visits, and propose simple checklists to improve uptake. Consider local cold-chain and availability constraints in rural settings.

Hypertension and cardiovascular risk

Appraisal: The 2022 hypertension guidance provides clear targets and therapeutic preferences appropriate for people with diabetes, emphasizing integrated risk management. (PubMed)

Suggestion: Incorporate population-level tools for ASCVD risk estimation validated for Indian cohorts, and provide decision aids for initiating combination antihypertensive therapy, including replication of simplified BP targets for older adults and those with CKD.

HOW RSSDI COMPARES WITH INTERNATIONAL GUIDELINES

RSSDI's core principles—individualized glycaemic targets, lifestyle first, early intensification, cardiometabolic risk reduction—align well with ADA/EASD. Where RSSDI differs, it usually reflects pragmatic considerations (cost, accessibility) and tailoring to Indian epidemiology. However, RSSDI would benefit from explicit crosswalks showing where guidance aligns or diverges from ADA/EASD/WHO, with rationale (e.g., resource constraints, prevalence differences, local trial data).

Implementation challenges in India

1. **Device and medication affordability.** High out-of-pocket costs limit CGM and novel agent uptake.
2. **Human resources and training.** Widespread use of CGM/insulin titration requires trained nurses/educators.
3. **Heterogeneous care delivery.** Large public/private mix, variable access to specialists.
4. **Patient factors.** Health literacy, cultural dietary patterns, and competing health priorities affect adherence.
5. **Data systems.** Lack of robust EMR/registry systems impedes audit and quality improvement.

RSSDI can mitigate these by producing implementation toolkits, training curricula, and advocating for inclusion of key interventions in national insurance/programme packages.

RESEARCH AND POLICY PRIORITIES EMERGING FROM THE APPRAISAL

1. **Cost-effectiveness analyses** for CGM, SGLT-2 inhibitors, GLP-1 RAs, and vaccination strategies in Indian settings.
2. **Implementation trials** of resource-stratified care pathways in primary care and district hospitals.

3. **Outcomes registries** to monitor real-world effectiveness and safety of newer therapies in Indian populations.
4. **Guideline methodology improvements**, including adopting formal evidence-grading (e.g., GRADE) and publishing full methods and search strategies.
5. **Equity analyses** to ensure recommendations are feasible across socioeconomic strata and geographies.

RECOMMENDATIONS FOR FUTURE RSSDI GUIDELINE CYCLES

1. **Standardize methodological reporting.** Publish methods, search strategies, conflict-of-interest declarations, and grades of recommendation.
2. **Implement resource-stratified algorithms.** Provide separate, prioritized care pathways for primary, secondary, and tertiary settings.
3. **Include economic analyses.** Even simple budget-impact models will help policy makers and hospital administrators.
4. **Produce implementation toolkits.** Flowcharts, order sets, patient leaflets in regional languages, training modules for allied health.
5. **Measure impact.** Recommend audit metrics and support pilot projects to evaluate uptake and outcomes.
6. **Frequent, focused updates.** Use living-guideline approaches for fast-moving areas (glucose monitoring technology, SGLT-2/GLP-1 indications).

CONCLUSION

The **RSSDI 2022 Clinical Practice Recommendations** represent a **scientifically grounded and locally relevant synthesis** of diabetes management in India. While its clinical applicability is strong, future updates should strengthen **methodological transparency, grading of evidence, and stakeholder inclusiveness** to enhance credibility and international comparability. RSSDI guidance plays an essential role in addressing India's diabetes burden by translating evidence into context-sensitive recommendations. Recent documents (2022–2024) expand coverage on monitoring, vaccinations, and cardiovascular risk, and emphasize pragmatic implementation. To maximise impact, RSSDI should formalize guideline methodology, provide explicit resource-stratified pathways, incorporate economic considerations, and deploy implementation toolkits. Doing so will improve uptake across India's heterogeneous health systems and better translate recommendations into improved patient outcomes.

ACKNOWLEDGEMENTS

This appraisal used RSSDI publications and related literature available on the RSSDI website and indexed journals. Key source documents reviewed include RSSDI Clinical Practice Recommendations (2022), RSSDI Expert Consensus for Optimal Glucose Monitoring (2024), RSSDI vaccination update (2024), and RSSDI hypertension guidance (2022). (rssdi.in)

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5. RSSDI Consensus documents on insulin therapy and related topics (2019 onwards). (rssdi.in)

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Section 06

Section Editor : **Bikash Bhattacharjee**

Therapeutics: Special Groups in Diabetes

Chapter 17

Therapeutic considerations in children and adolescents with type 2 diabetes

Bipul Kumar Choudhury

INTRODUCTION

Diabetes mellitus is a complex and chronic metabolic disorder of carbohydrate metabolism that occurs primarily due to defect in insulin secretion, action or both. It results in chronic hyperglycaemia and needs continuous lifelong medical care. Diabetes mellitus is known to affect all age groups and it has been observed that the age-specific prevalence of diabetes consistently increases with age. Diabetes in children and adolescents indicates onset of diabetes before the age of 18 years.

Worldwide the incidence and prevalence of type 2 diabetes in children and adolescents vary substantially among countries, age categories and ethnic groups. The overall prevalence is around 13 to 14%. India along with China and America have the highest estimated number of incident cases. In 2025 the *Ministry of Statistics and Programme Implementation* (MoSPI), *Government of India,* report, "Children in India 2025", found that the national prevalence of diabetes in children aged 10-19 years is 0.6%. In a nationwide screening campaign by Mohan et al, the overall prevalence of diabetes in India among those below 25 years of age was found to be 9.8%.

The aetiology of diabetes is heterogeneous amongst children. The most common causes of diabetes amongst children are Type 1 and Type 2 diabetes. Type 1 is the most common form of young-onset diabetes in many populations, especially those of European ancestry. However, type 2 diabetes is becoming more common particularly in certain high risk population like those with obesity, strong family history of diabetes etc. Type 2 diabetes has also been observed in pre-pubertal children under the age of 10 years.

SPECTRUM

Children with type 2 diabetes differ from adults in respect to pathophysiology and response to therapy. Studies have shown that there is rapid progression of beta cell dysfunction in children. They also develop complications early. Long term follow-up data from the Treatment Option for Type 2 Diabetes in Adolescents and Youth (TODAY) study has shown that most patients with onset of type 2 diabetes at a young age develop microvascular complications by young adulthood. So early identification of Type 2 Diabetes in Adolescents and children is very important. Screening for type 2 diabetes can be done after onset of puberty or after 10 years of age in youth who have a body mass index (BMI) ≥85th percentile for age and sex and risk factors for type 2 diabetes.

The diagnostic criteria for diabetes in children are same as in adults and are based on blood glucose measurements and the presence or absence of symptoms. Symptoms of hyperglycaemia and one of the following laboratory values and negative islet autoantibodies, suggests type 2 diabetes in children-

- FPG ≥126 mg/dl
- 2-hour plasma glucose on an OGTT ≥200

mg/dl.OGTT:1.75 g/kg (max 75 g) anhydrous glucose dissolved in water

- Random plasma glucose ≥200 mg/dl
- HbA1c ≥ 6.5% by a NGSP-certified device, standardized to the DCCT assay

After the initial step of diagnosing diabetes, the differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both therapeutic decisions and educational approaches. Surveys in India show high rates of overweight and obesity ranging from 1.5% to over 24% amongst children. And hence at times distinguishing type 1 from type 2 diabetes becomes difficult. Whereas obesity is common amongst type 1 diabetes, diabetes associated auto antibodies and ketosis may also be present in type 2 diabetes.

MANAGEMENT PLAN

Management of type 2 diabetes in children and adolescents includes lifestyle modification, **Diabetes Self-Management Education and Support** (DSMES) and pharmacological intervention. At the onset of diabetes, the main goal of treatment remains glycaemic control and correction of metabolic derangements irrespective of the ultimate type of diabetes.

Once a child is diagnosed with type 2 diabetes, his or her parents and family members should be properly counselled about the illness and need of regular treatment and follow up. Both the patient and their parents should be educated regarding balanced diet, need of exercise and maintaining optimum weight for proper growth and development. Nutritional advice should be culturally appropriate and counselling should be done regarding living with diabetes. All patients should be advised aerobic, muscle strengthening and bone strengthening exercise. They should do at least 60 min of moderate to vigorous physical activity daily with muscle and bone strength training at least 3 days a week. They should also reduce sedentary time like watching TV, computer-related activities, texting, and video games to less than 2 hours a day.

Pharmacologic treatment option are limited and includes Insulin, Metformin, Glucagon Like Peptide 1(GLP 1) receptor agonists, and sodium glucose cotransporter 2(SGLT 2) inhibitors. The target HbA1c for type 2 diabetes is <6.5% in children compared to <7%for type 1 diabetes.

Insulin: Insulin is a key treatment for type 2 diabetes in children, especially at the time of diagnosis when hyperglycaemia is severe. It has been observed that obese children with type 2 diabetes often present with ketoacidosis or marked ketosis. Such patients should be treated with insulin initially. Once ketoacidosis or ketosis is resolved, oral hypoglycaemic agents like metformin can be added. The insulin dose can then be tapered gradually and dose of metformin increased. Insulin also remains the initial treatment when there is diagnostic dilemma between type 1 and type 2 diabetes in a patient with high blood glucose levels above 250 mg/dl or HbA1c more than or equal to 8.5%.

Metformin: Metformin is the most common oral hypoglycemic agent used in children with type 2 diabetes. In patients who do not need insulin initially can be put on Metformin. It is approved for age > 10 years. Metformin can be started at a dose of 500 mg once or twice daily and the maximum dose is 2000 mg per day. It is well tolerated and alone has been shown to achieve durable glycaemic control.

GLP 1 receptor agonist: GLP 1 receptor agonist (GLP-1RA) are another class of medicines approved for use in children above 10 years of age. They are safe, effective and promotes weight loss. In 2019, liraglutide became the first GLP-1RA approved for youth with type 2 diabetes, followed by Exenatide in 2021 and Dulaglutide in 2022.

SGLT 2 inhibitors: Sodium glucose cotransporter 2(SGLT 2) inhibitors are also approved in youths with type 2 diabetes. The FDA has approved Dapagliflozin and Empagliflozin for children and

adolescents aged 10 and older with type 2 diabetes. When prescribed, proper genital hygiene should be emphasised in such patients.

As in adults all children and adolescents diagnosed with type 2 diabetes should be evaluated for comorbidities like hypertension and for presence of any complications. Blood pressure should be measured at diagnosis and at every subsequent visit. Echocardiographic evaluation is recommended in youth with confirmed hypertension to assess for left ventricular target organ injury. The initial pharmacological treatment for hypertension should be monotherapy with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker and the dose should be increased to achieve a BP in the normal range. Secondary hypertension should be looked for if BP remains persistently high even after optimum medication. Testing for dyslipidaemia should occur once glycaemic control has been achieved or after 3 months of initiation of medication regardless of HbA1c values, and annually thereafter unless abnormal. Statins should be initiated in youth who continue to have LDL levels >130 mg/dl after a 6-month trial of lifestyle change intervention. Statin therapy has been shown to be safe and effective and should be the first pharmacologic intervention for dyslipidaemia. If LDL is <130 mg/dl but triglyceride levels are >400 mg/dl, fibrates should be initiated. Albuminuria screening should be done at diagnosis and annually thereafter. Liver enzymes alanine transaminase and aspartate aminotransferase should be measured at diagnosis and annually thereafter. Symptoms of obstructive sleep apnoea should be assessed at diagnosis and annually thereafter for all overweight and obese children. All girls with type 2 diabetes should be evaluated for polycystic ovarian syndrome (PCOS). A thorough menstrual history and necessary biochemical investigations should be done. PCOS screening should occur at diagnosis in pubertal girls and yearly thereafter. Retinopathy and neuropathy screening should be done at the time of initial diagnosis and then annually. Proper foot care should be emphasized. Children with type 2 diabetes should be screened for psychological comorbidities including depression, diabetes distress, and disordered eating at diagnosis and at regular follow-up intervals. Patients should be educated about hypoglycaemia, its symptoms and management. Hypoglycaemia should be treated with oral glucose. An immediate source of glucose must always be available to young people with diabetes.

CONCLUSION

Type 2 diabetes is increasing in children and adolescents. They differ from adults in respect to pathophysiology and occurrence of complication. At the time of diagnosis both the patient and their parents should be educated about lifestyle modification and need for regular treatment. Insulin along with Metformin, GLP -1 RA and SGLT 2 inhibitors are approved for use in children with type 2 diabetes. Comorbidities and complications should be looked for at the time of diagnosis and thereafter at regular intervals.

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Chapter 18

Management Considerations in Older Adults with Diabetes

Hemanga Barman

INTRODUCTION

There are growing proportion of older adults among those with diabetes worldwide and overall population with diabetes in 2012 were aged 60-79 years. This proportion was expected to reach 41% by the year 2023 and more than 252 million older adults with diabetes by 2035, according to estimate from 2013 IDF Diabetes Atlus. This numbers will be more at present than expected. Management of older patients with diabetes is complicated by medical and functional heterogenicity of this group. The heterogenicity of this population is a key consideration for clinicians developing intervention strategies and establishing targets for elderly patients with diabetes.

PATHOPHYSIOLOGY

Aging is combined with alterations in glucose metabolism including insulin secretion, resistance, and hepatic glucose metabolism. In addition, condition associated with aging such as co-existing illness, increase adiposity, decrease physical activity, sarcopenia, and effect self-medication used to treat comorbidities further impact abnormal glucose metabolism in the elderly. Auto immunity has shown to play a role in the impairment of glucose induced insulin secretion in lean older people with diabetes. Pro-inflammatory cytokines such TNF alfa and c-reactive protein have been associated with higher risk of diabetes in elderly patient. On the other hand, adiponectin was found to be associated with lower risk of diabetes in older man and women. Age associated reduction in mitochondrial oxidative and phosphorylation activity have also been shown to contribute insulin resistance in elderly. Low level of Testosterone in men and higher level of Testosterone in women are associated with higher risk of insulin resistance and diabetes in elderly.

CHALLENGES AND MANAGEMENT

The goal of physician should be to optimized glycaemic control and reduce associated cardiovascular risk factors in an effort to maximize long term quality of life. On the other hand, frail older patients particularly those with severe co-morbidities and disabilities, aggressive management is not likely to provide benefits and may even result in harm as a consequence of frequent hypoglycemia associated with aggressive glycemic control. In these patients the regimen should be simplified with less frequent dosing, avoiding interaction with other drugs that may affect the treatment effectiveness. The presence of renal, liver and/or cardiovascular comorbidities may create contraindication and/or increase the risk of hypoglycemia. Other important considerations are cost and effect of these medication on weight and lipids. In general, oral agent should be started at the lowest possible effective doses to minimize the risk of adverse events.

Geriatric syndrome—Many co-existing medical conditions (such as cognitive dysfunction, depression, functional disability, falls,

polypharmacy, urinary incontinence, and chronic pain) not typically associated with diabetes occur at higher frequency in older adult with diabetes. These condition term as geriatric syndrome may interfere with a patient ability to perform self-care task, including glucose monitoring, understanding the role of diet and exercise in glucose metabolism and following a complex insulin regimen. Difficulty with self-management may lead to increased risk of non-adherence or treatment errors contributing to an increase risk of hypoglycemia and poor glycemic control, which intern leads to further difficulty with self-management and ultimately increase risk of morbidity and mortality. Thus, before developing treatment and management plans for older adults, it is of key importance to conduct a careful and comprehensive assessment for all potential comorbidities which will very possibly impact how we plan our therapeutic approach.

Cognitive impairment _diabetes is associated with 1.5 fold greater risk of cognitive declined and 1.6 fold increase risk of future dementia. Cognitive dysfunction in older adults with diabetes may manifest as deficit in psychomotor efficiency, global cognition, episodic memory, semantic memory, and working memory. In particular, executive functioning which is mediated by frontal lobe, effect behaviour such as problem solving, planning, organisation, insight reasoning and attention. Cognitive dysfunction can interfere with self-care abilities such as following medical nutritional and exercise regimes leading to increased risk of treatment complication. Again, depression is twice as common in people with diabetes compared to the general population. It is associated with poor glycemic control, poor adherence to medication and diet regime, a reduction in quality of life and an increase in health care expenditure.

Impact of Polypharmacy

This is a complex and challenging aspect of caring adult. Multiple medications are unavoidable in many associated conditions and careful attention is needed for appropriate dosing and avoidance of drug-drug interaction. Assessment of financial feasibility are important. Individuals with physical disability may require assistance from other caregivers or family member to do SMBG, giving insulin injection, meal preparation, and following a physical activity regime. Falls, urinary incontinence, chronic pain also having impact with older patient with diabetes.

Present Medication for day to day diabetes management in older adults

1. Insulin has marginal risk of hypoglycemia and weight gain, but will be less with newer insulin analogue.
2. GLP 1 and GIP agonists in both oral or injectable are costly but safe for older adult with cardiovascular and renal benefit.
3. SGLT 2 inhibitors have cardiovascular and renal benefit but to be careful for incidence of urinary problem.
4. DPP-4 inhibitors are safe and devoid of hypoglycemia, do not interference with cardiac and renal outcome.
5. Glitazones are safe, but careful with prostatic problem, post-menopausal women. They are not used in patients with heart failure.
6. Sulphonylureas of newer generation like glimiperide or extended release gliclazide are generally safe with less weight gain but with some risk of hypoglycaemia.

To conclude, management in older adults with diabetes should be individualised with consideration of hypoglycaemia, life expectancy, cardiovascular and renal benefit.

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Chapter 19

Management of Diabetes in Pregnancy

Suranjit Barua
Harshdeep V Nariya

INTRODUCTION

Diabetes in pregnancy includes both Pregestational diabetes (Type 1 and Type 2 Diabetes mellitus) and Gestational Diabetes mellitus (GDM), and it presents significant challenges due to associated maternal and foetal risks, which are largely related to the degree of hyperglycaemia, chronic complications, and underlying comorbidities. Specific risks associated with diabetes in pregnancy encompass a range of adverse outcomes, such as spontaneous abortion, preeclampsia, foetal anomalies, foetal demise, macrosomia, neonatal hypoglycaemia, neonatal hyperbilirubinemia and neonatal respiratory distress syndrome.

PRECONCEPTION COUNSELLING AND CARE

Preconception counselling is a critical component of care for all individuals with diabetes who have child-bearing potential. This counselling should incorporate a discussion of family planning, including the importance of using effective contraception until the individual's treatment plan and HbA1C are optimized for pregnancy. A primary goal of preconception counselling is to emphasize the importance of achieving glucose levels as close to normal as safely possible prior to conception. Observational studies have established that an elevated periconceptional A1C is directly proportional to an increased risk of congenital anomalies, particularly affecting the kidneys, heart (congenital heart disease), and nervous system (anencephaly, microcephaly and caudal regression). Organogenesis occurs primarily between 5–8 weeks of gestation; thus, optimizing glycemia prior to conception is vital. Ideally, the A1C goal for conception should be less than 6.5% (less than 48 mmol/mol), as this threshold is associated with the lowest risks of congenital anomalies, preeclampsia, and preterm birth.

GLYCAEMIC GOALS AND MONITORING FOR DIABETES IN PREGNANCY

During pregnancy, Self-Monitoring of blood glucose (SMBG) is recommended to achieve optimal glucose levels, including fasting, pre-prandial, and postprandial measurements. At least minimum four times a day Glucose Monitoring must be taken, daily fasting and two hours after each meal. The established target goals for pregnant individuals with Type 1, Type 2, or gestational diabetes are strict:

- Fasting plasma glucose: <95 mg/dL (<5.3 mmol/L).
- One-hour postprandial glucose:<140 mg/dL (<7.8 mmol/L).
- Two-hour postprandial glucose:<120 mg/dL (<6.7 mmol/L).

In addition to SMBG, continuous glucose monitoring (CGM) when accessible and affordable/acceptable, can be used to measure glycaemic fluctuation, which may be linked to

macrosomia specially in Type 1 diabetes mellitus. The HbA1C goal in pregnancy is ideally less than 6.0% (<42 mmol/mol) if it can be safely achieved without significant hypoglycaemia. Due to the physiological increase in red blood cell turnover during normal pregnancy, A1C is slightly lower and may fall. Consequently, HbA1C should be used as a secondary measure of glycaemic outcomes, monitored perhaps monthly, as postprandial hyperglycaemia (which drives macrosomia) may not be fully captured by HbA1C. The recommended hypoglycaemia threshold during pregnancy is blood glucose <70 mg/dL (<3.9 mmol/L).

MANAGEMENT OF PREGESTATIONAL DIABETES (PGD)

Guidelines of the American Diabetes Association recommend insulin as the first-line medication to treat Type1 and Type2 diabetes mellitus, and metformin is only indicated in women who persist with poor glycaemic control after dietary interventions and exercise and who refuse insulin treatment in Type2 diabetes mellitus. Other oral hypoglycaemic agents including glyburide to be avoided in management of Diabetes during pregnancy. Both multiple daily insulin injections and continuous subcutaneous insulin infusion (insulin pump technology) are reasonable delivery strategies. Basal bolus therapy is most effective in helping achieve these tight glycaemic targets. Detemir and NPH remain the preferred basal insulins, while rapid acting insulins like Aspart and Lispro are used for postprandial coverage. Regular Insulin also can be used for postprandial coverage. Glargine and Degludec may be considered if used before conception with good control, but should not be newly initiated due to limited pregnancy data and both are not yet approved by FDA.

Pregnant individuals with Type 1 diabetes experience altered insulin requirements throughout gestation. Early pregnancy may show enhanced insulin sensitivity and lower glucose levels, potentially increasing the risk of hypoglycemia. However, beginning around 16 weeks, insulin resistance increases, leading to a linear rise in total daily insulin doses (approximately 5% per week) through week 36, often resulting in a doubling of prepregnancy requirements. Pregnancy is a ketogenic state, putting individuals with Type 1 diabetes (and to a lesser extent Type 2 diabetes) at risk for diabetic ketoacidosis (DKA) even at lower blood glucose levels than in the nonpregnant state. DKA carries a high risk of stillbirth. Patients should receive education on DKA prevention and detection, including obtaining ketone test strips.For Type 2 diabetes, optimal glycemic goals may be easier to achieve than with Type 1 diabetes but often require much higher doses of insulin. Follow-up of off-spring from the Metformin in Women with Type 2 Diabetes in Pregnancy trial showed no differences in anthropometrics of children at 24 months.

Individuals with pre-existing diabetic retinopathy require close monitoring during pregnancy to assess for stability or progression of the condition. Dilated eye examinations should ideally occur before pregnancy or in the first trimester. Subsequently, pregnant individuals should be monitored every trimester and for one year postpartum, as recommended by the eye care professional and indicated by the degree of retinopathy.

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS (GDM)

GDM is associated with increased risks of large-for-gestational-age birth weight, neonatal and pregnancy complications, long-term maternal Type 2 diabetes, and abnormal glucose metabolism in offspring.

- **Non-Pharmacological Therapy for GDM**

Lifestyle behaviour change, including medical nutrition therapy (MNT) and physical activity are the essential first step in managing GDM, and it may suffice as the sole treatment for many individuals. MNT for GDM includes a meal plan providing adequate nutrition while ensuring appropriate weight

gain and foetal well-being to meet increased requirements of energy, protein, and micronutrients, achieve normoglycemia, and also prevent ketosis. The nutrition plan should emphasize nutrient-dense, whole foods, including fruits, vegetables, legumes, whole grains, and healthy fats with omega-3 fatty acids (like nuts, seeds, and fish), while limiting processed foods, fatty red meat, and sweetened foods. Simple carbohydrates lead to higher post-meal excursions. Severe dietary restrictions, such as the ketogenic diets, should be avoided.

- **Pharmacologic Therapy for GDM**

If lifestyle management alone is insufficient to meet glycaemic goals, insulin should be added. NPH Insulin (isophane Insulin) is first line long acting Insulin during pregnancy, especially when starting Insulin in newly diagnosed GDM. Insulin is the preferred medication for treating hyperglycaemia in GDM. When insulin cannot be utilized and cost, storage, and compliance are logistical concerns and If a pregnant woman is unwilling to take insulin or cannot use insulin, metformin can be prescribed only after weighing the benefits and drawbacks.

The contemporary information regarding Use of Metformin in Diabetes in pregnancy

According to the 2020 Metformin in women with Type 2 diabetes in pregnancy (MITy) trial, using metformin while pregnant did not result in any significant side effects. MiG TOFU trial revealed that metformin or insulin for GDM was associated with similar offspring total and abdominal body fat percent and metabolic measures at 7–9 years. Metformin-exposed children were larger at 9 years. Metformin might interact with fetal environmental factors to influence offspring outcomes. NICE Guidelines state that the use of metformin as an adjunct or alternative to insulin in the preconception period and during pregnancy when the likely benefit from improved blood glucose control outweighs the potential for harm.

POSTPARTUM CARE

Postpartum, insulin sensitivity increases dramatically with the delivery of the placenta, and insulin requirements often drop rapidly to roughly half the pre-pregnancy requirements for the initial few days. Careful attention is needed to prevent hypoglycaemia, especially in the setting of breastfeeding and erratic schedules.

CONCLUSION

Individuals diagnosed with GDM must be screened for persistent diabetes or prediabetes at 4–12 weeks postpartum using the 75-g oral glucose tolerance test (OGTT) and clinically appropriate non-pregnancy diagnostic criteria. Individuals with a history of GDM have a high lifetime maternal risk for Type 2 diabetes (estimated at 50–60%). Therefore, lifelong screening for Type 2 diabetes or prediabetes should occur every 1–3 years. Those with pre-gestational diabetes should continue insulin therapy with modification of doses. Finally, breastfeeding is recommended for all individuals with diabetes, including those with a history of GDM, as it confers numerous health benefits to the baby and reduces the mother's risk for Type 2 diabetes later in life.

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Section 07

Section Editor : **Debaprasad Chakrabarti & Dipankar Prakash Bhaumik**

Therapeutics: Oral Antidiabetic Drugs

Chapter 20

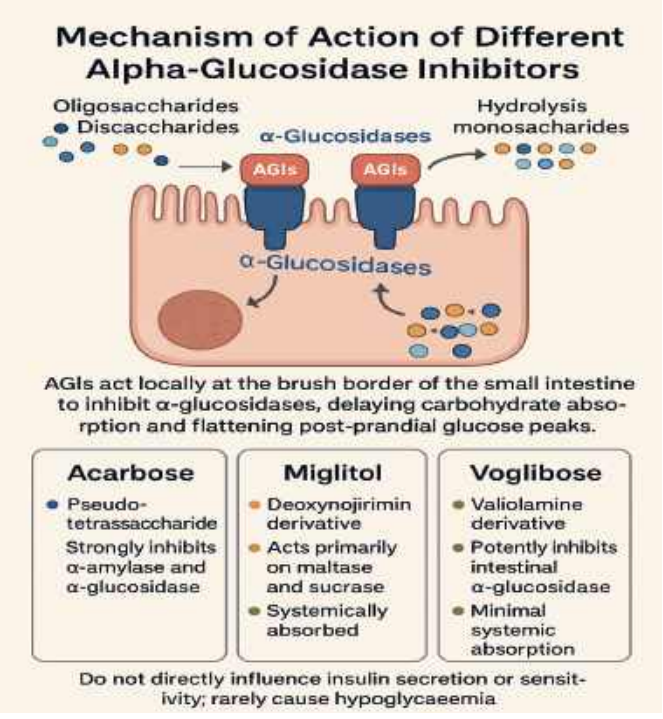
Relevance of Alpha Glucosidase Inhibitors in Indian Scenario

Karuna K Barman
Samik Deb

INTRODUCTION

Alpha-glucosidase inhibitors (AGIs) are a class of oral antidiabetic agents that act locally in the intestinal mucosa to delay carbohydrate digestion and absorption, thereby attenuating post-prandial hyperglycaemia (PPHG). The principal drugs are Acarbose, Voglibose, and Miglitol. Although introduced more than three decades ago, their role has been re-evaluated in recent years, particularly in populations such as India, where dietary patterns and pathophysiology make post-meal hyperglycaemia a prominent component of type 2 diabetes mellitus (T2DM).

MECHANISM OF ACTION



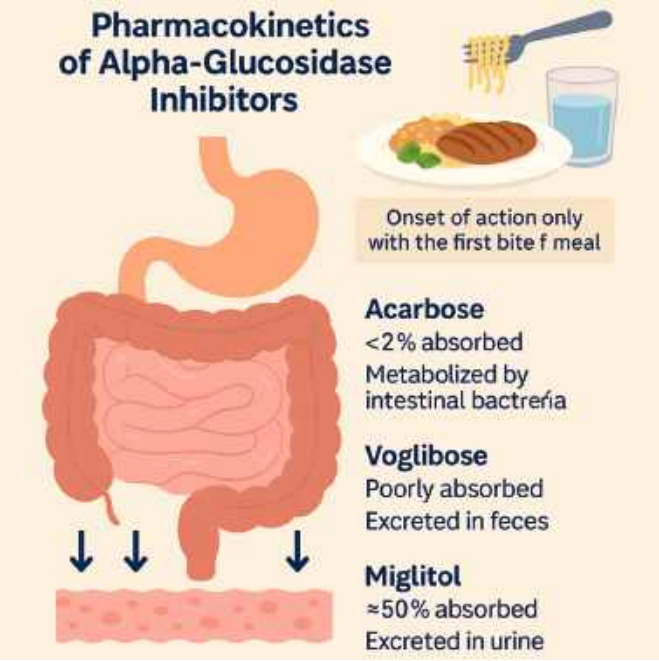
Alpha-glucosidase inhibitors (AGIs) act locally at the brush border of the small intestine, where they competitively and reversibly inhibit alpha-glucosidases such as maltase, sucrase, isomaltase, and glucoamylase. These enzymes catalyse the final step in carbohydrate digestion—hydrolysing oligosaccharides and disaccharides into absorbable monosaccharides (mainly glucose). By delaying this process, AGIs slow carbohydrate absorption, flattening post-prandial glucose peaks.

Acarbose is a pseudo-tetrasaccharide that strongly inhibits both alpha-amylase (in pancreatic secretions) and intestinal alpha-glucosidase, making it effective for high-starch diets.

Miglitol, a deoxy-nojirimycin derivative, resembles glucose and acts primarily on maltase and sucrase. It is systemically absorbed but rapidly excreted unchanged in urine. Voglibose, a Vali olamine derivative, has potent intestinal alpha-glucosidase inhibition with minimal systemic absorption, leading to fewer systemic effects and good gastrointestinal tolerance. Because the mechanism is local and non-systemic, AGIs do not directly influence insulin secretion or sensitivity and therefore rarely cause hypoglycaemia when used alone.

PHARMACOKINETICS AND PHARMACODYNAMICS

Acarbose is minimally absorbed (<2%) and metabolised mainly by intestinal bacteria; its systemic exposure is negligible. Voglibose is also



poorly absorbed and predominantly excreted unchanged in faeces. Miglitol is absorbed to a greater extent (≈50%) and excreted unchanged in urine. The onset of action occurs only when taken with the first bite of a meal, as enzyme inhibition must coincide with carbohydrate entry into the intestine.

Efficacy in Glycaemic Control

HbA1c and PPG Reduction

Meta-analyses have demonstrated modest but consistent HbA1c lowering of 0.5–1.0 %, with more substantial reductions in 2-hour PPG excursions (≈60–80 mg/dL) The Indian subgroup of the GlucoVIP study (n ≈ 1,996) reported a mean HbA1c reduction of 1.0 % and a 2-h PPG reduction of 74 mg/dL after 12 weeks of acarbose therapy, confirming efficacy in the Indian population. **Recent evidence further supports** the presence of AGIs in Asian populations. A 2022 multicentre real-world study from South Korea demonstrated that adjunctive voglibose therapy with metformin significantly improved post-prandial glucose and reduced glycaemic variability in patients with early T2DM.Similarly, a 2023 Japanese cohort analysis reported improved post-meal glucose control and reduced progression to insulin therapy when AGIs were added early in treatment.

Comparison with Other Oral Agents

Compared with sulfonylureas or metformin, AGIs exert smaller overall HbA1c reductions but specifically target post-prandial spikes. They are weight-neutral and do not increase the risk of hypoglycaemia, making them attractive for early or combination therapy where PPG predominates.

CLINICAL BENEFITS BEYOND GLUCOSE LOWERING

1. **Reduced glycaemic variability**: By smoothing post-prandial surges, AGIs minimise oxidative stress and endothelial dysfunction.

2. **Potential cardiovascular benefit**: In the STOP-NIDDM trial, acarbose reduced progression to diabetes and cardiovascular events among subjects with impaired glucose tolerance (IGT). This potential for cardiovascular risk reduction adds another layer of benefit to the use of AGIs.

3. **Weight neutrality**: Unlike sulfonylureas or thiazolidinediones, AGIs do not cause weight gain. This weight neutrality can be a significant advantage for patients who are concerned about weight management.

4. **Alpha-Glucosidase Inhibitors and Gut Microbiota:** Alpha-glucosidase inhibitors (acarbose, voglibose, miglitol) beneficially modulate gut microbiota by increasing the undigested carbohydrates that reach the colon, thereby enhancing the growth of Bifidobacterium, Lactobacillus, and Akkermansia, raising short-chain fatty acids (butyrate, propionate) that improve insulin sensitivity, gut integrity, and reduce inflammation. These microbiota-mediated effects partly explain AGIs' metabolic benefits beyond glucose control. In Indian patients with high-carbohydrate diets and dysbiosis, AGIs not only target post-prandial hyperglycaemia but also restore microbial

balance, supporting metabolic health and complementing metformin or dietary fibre therapy for optimal glycaemic and gut outcomes.

5. Alpha-Glucosidase Inhibitors and GLP-1: Alpha-glucosidase inhibitors (AGIs) enhance glucagon-like peptide-1 (GLP-1) secretion by delaying carbohydrate absorption in the small intestine. This results in increased delivery of undigested carbohydrates to the distal ileum and colon, stimulating L-cells to release GLP-1. Clinical and experimental studies show that AGIs increase endogenous GLP-1 by 2- to 3-fold. Thus, AGIs not only reduce post-meal hyperglycaemia but also augment.

Incretin response, offering additive benefits when combined with DPP-4 inhibitors or GLP-1 receptor agonists. New mechanistic work has highlighted that AGIs also improve gut endocrine signalling. A 2023 mechanistic study confirmed enhanced GLP-1 and PYY release with acarbose use, demonstrating improved satiety and delayed gastric emptying (Singh et al. 2023). These findings reinforce the metabolic and incretin benefits of AGIs beyond glucose control.

6**. Safety in elderly and mild renal impairment**: Minimal systemic absorption makes them suitable for older adults, provided renal function is not severely compromised.

However, these benefits have not translated into large-scale cardiovascular outcomes trials (CVOTs) comparable to those of SGLT2 inhibitors or GLP-1 receptor agonists.

ADVERSE EFFECTS AND LIMITATIONS

The most common adverse effects—flatulence, abdominal distension, and diarrhoea—result from fermentation of unabsorbed carbohydrates by colonic bacteria. These can be minimised by:

Starting at a low dose (acarbose 25 mg BID or voglibose 0.2 mg BID), gradual titration, and advising patients to reduce their intake of refined carbohydrates. Transient elevation of hepatic transaminases and rare cases of hepatotoxicity have been reported with high-dose acarbose. AGIs have little effect on fasting plasma glucose and therefore are less effective when fasting hyperglycaemia predominates. Contraindications include inflammatory bowel disease, intestinal obstruction, malabsorption syndromes, and severe renal or hepatic impairment.

DOSING AND ADMINISTRATION

Drug	Typical Starting Dose	Titration	Maximum Dose	Remark
Acarbose	25 mg with each main meal	Increase every 4–8	50–100 mg TID	Avoid if serum creatinine > 2 mg/dL
Voglibose	0.2 mg TID with meals	May increase to 0.3 mg TID	0.3 mg TID	Widely used in India.
Miglitol	25 mg TID	Up to 100 mg TID	100 mg TID	Avoid in severe renal impairment

Administration with the first bite of each meal is essential. Skipping a meal means skipping that dose.

INDIAN CONTEXT AND RELEVANCE

Epidemiological and Dietary Considerations

Indian patients with T2DM characteristically have: High carbohydrate intake (60–70 % of calories), multiple daily meals with high glycaemic load, Early post-prandial hyperglycaemia is even lower in prediabetic states, relative to Western populations. These features make post-meal glucose control a significant determinant of overall HbA1c. Therefore, drugs targeting PPG—like AGIs are particularly suited to the Indian diet and glycaemic pattern.

Clinical Evidence in Indian Patients

GlucoVIP Indian subgroup: Acarbose reduced HbA1c by 1 % and PPG by ≈ 74 mg/dL in 12 weeks.

Voglibose Indian trials: Multiple short-term studies

demonstrated similar efficacy and tolerability.

Real-world data: Observational analyses confirm better PPG control when AGIs are added to metformin or sulfonylureas in Indian clinics. Recent data from an Indian tertiary-care cohort also showed significant improvement in 2-hour PPG and glycaemic variability with voglibose add-on therapy, particularly among high-carbohydrate diet consumers.

INDIAN CLINICAL PRACTICE GUIDELINES

RSSDI Clinical Practice Recommendations 2022

The Research Society for the Study of Diabetes in India (RSSDI) places AGIs among oral glucose-lowering agents helpful when post-prandial hyperglycaemia is predominant. Key statements include:

"AGIs may be used as monotherapy in patients intolerant to metformin or as add-on therapy targeting post-prandial glucose. "They are weight-neutral and have minimal risk of hypoglycaemia. "Avoid use when serum creatinine > 2 mg/dL or in significant gastrointestinal disease."

Endocrine Society of India / RSSDI-ESI Consensus (2020)

The joint consensus emphasises that "post-prandial hyperglycaemia contributes significantly to total glycaemic load in Asian Indians; α-glucosidase inhibitors are rational choices where carbohydrate rich foods prevail." They are particularly noted for use in early diabetes or prediabetes settings to flatten PPG excursions.

Use in Combination Therapy

Because AGIs act via the intestinal lumen and have complementary mechanisms to other OADs, they can be effectively combined with:

- Metformin: addresses hepatic insulin resistance (fasting glucose) + AGI for PPG → synergistic HbA1c reduction.
- Sulfonylureas or DPP-4 inhibitors: useful when fasting control is achieved but post-meal spikes persist.
- Insulin therapy: AGIs may reduce post-meal insulin requirements in basal-bolus regimens.

They should not be combined with complex carbohydrate digestive enzymes (e.g., amylase supplements) or in patients on very low-carbohydrate diets.

AGIS IN PREDIABETES AND PREVENTION OF DIABETES

The STOP-NIDDM trial (Chiasson JL et al., Lancet 2002) demonstrated that acarbose reduced progression from IGT to diabetes by ≈ 25 %. Indian guidelines allow the use of AGIs in IGT or prediabetes when lifestyle modification alone fails to normalise. Given that Indian populations develop dysglycaemia at lower BMI and younger ages, this preventive role may be especially relevant. Updated evidence suggests that preventive benefits remain relevant in Asian populations. A Chinese trial published in 2022 demonstrated that low-dose acarbose significantly reduced progression from impaired glucose tolerance to diabetes over 18 months (Zhou et al. 2022).

SAFETY AND CONTRAINDICATIONS

Contraindication / Caution	Rationale / Note
Inflammatory bowel disease, colonic ulceration	Gas accumulation and risk of distension intestinal obstruction
Chronic intestinal disorders with malabsorption	Exacerbation of symptoms
Serum creatinine > 2 mg/dL or eGFR < 25 Limited safety data;	risk of accumulation mL/min (especially miglitol)
Hepatic impairment (especially acarbose)	Monitor LFTs
Pregnancy/lactation	Limited data; avoid unless essential
Paediatric Use	Not routinely recommended
Adverse effects are usually dose-related	Reversible upon discontinuation.

CONCLUSION

AGIs (acarbose, voglibose, miglitol) act by inhibiting intestinal α-glucosidase enzymes, reducing post-prandial glucose absorption. They offer modest HbA1c reduction, are weight-neutral, and carry low risk of hypoglycaemia. Their most significant relevance lies in carbohydrate-rich diets and post-meal hyperglycaemia, making them highly suitable for Indian patients. Clinical trials and Indian data confirm their efficacy and tolerability. Gastrointestinal side effects and thrice-daily dosing remain practical limitations. In selected Indian patients, especially those with mild diabetes, prediabetes, or PPG-driven hyperglycaemia, AGIs provide a safe, effective, and economical therapeutic option.

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Chapter 21

DPP4 Inhibitors vs SGLT 2 Inhibitors: "Competitors or Partners"

Dinesh Agarwal
Bharat Bhushan Kukreja
Saurav Das

INTRODUCTION

On oral consumption of glucose, it was noted there was augmentation of insulin release compared to iv glucose administration. This effect was later discovered to be the result of a group of gut-derived hormones, known as the incretin effect. This was due to incretin-induced glucose dependent insulin secretion and glucagon suppression. These incretins, such as GIP and GLP1, are rapidly degraded by dipeptidyl peptidases. DPP4i prevent this degradation and prolong the action of these incretins. This results in suppression of endogenous glucose production and reduction in plasma glucose concentration. Sodium-glucose cotransporters (SGLT) are a group of secondary active transporters. Mainly 2 types- SGLT1 present in the small intestine and kidneys, and SGLT2 present in kidneys. Since SGLT2 is present in S1 and S2 segment of the proximal convoluted tubule where majority of glucose reabsorption occurs, this has been targeted with SGLT2i. The urinary glucose loss creates a negative energy balance. Due to the associated natriuresis, SGLT2i has been noted to have pleiotropic effects. Also, since this action is independent of insulin secretory status and reliant upon kidney function, it offers a separate avenue for glycemic control.

Type 2 Diabetes is caused by the amalgamation of deleterious effects of multiple pathophysiologic pathways, as noted initially by DeFronzo et al in the Ominous Octet. Effective management thus involves addressing these pathophysiologic pathways. In this respect, we are blessed with an expansive armamentarium in today's diabetes therapy landscape. But, with so many options available, it is common for physicians to be troubled while choosing an optimal combination. Dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) are two such drug classes.

To answer whether DPP4i and SGLT2i function synergistically as partners or compete against each other, we need to look at their mechanism of action.

COMPETITORS OR PARTNERS?

Which agent to choose first?

For a patient with higher cardiovascular risk or clinical ASCVD or nephropathy or MASLD, SGLT2i would be the preferred option. For the elderly or significant prostate-related issues or recurrent genital infections seeking postprandial glycemic control, DPP4i would be the better choice.

Since the mechanisms of action differ, there is no competition between the classes for efficacy or safety outcomes. And since the glycemic reduction is quite modest with both the classes, combination therapy has been advocated routinely. But, what may the benefits be?

Glycemic efficacy: Since both the drug classes offer modest glycemic efficacy with average HbA1c reductions of 0.6-1.0%, combining both classes enhances the glycemic control, albeit not to the extent

expected. Rosenstock et al (dapagliglifozin/ saxagliptin) and DeFronzo et al (empagliflozin/ linagliptin), in well-planned RCTs, noted that the combination therapy result in higher HbA1c reduction compared to either SGLT2i or DPP4i therapy alone. But, the glycemic benefit was lower than expected additive effect from individual component data. This is likely due to the stimulation of endogenous glucose production (EGP) by the negative energy balance created by SGLT2i. The effect of DPP4i on EGP is likely insufficient to negate this impact. The same was proved on subanalysis based on baseline HbA1c- where at higher baseline HbA1c (>9%), due to higher glycosuric effect and higher negative energy balance created by SGLT2i, the HbA1c reduction was markedly lower than the expected additive effect.

The expected additional HbA1c reduction also varies depending on the baseline therapy. Addition of SGLT2i to baseline DPP4i therapy has shown higher HbA1c reduction compared to addition of DPP4i to baseline SGLT2i therapy. The meta-analysis also noted that the combination therapy significantly reduced HbA1c while promoting modest weight loss compared to DPP4i alone, and significantly reduced HbA1c with no significant effects on body weight compared to SGLT2i alone. Compared to either monotherapy, fasting plasma glucose lowering was higher with combination therapy. SGLT2i addition at higher baseline HbA1c (>8.5%) showed a higher reduction in HbA1c, as expected due to the higher urinary glucose losses at higher plasma glucose levels. Risk of hypoglycemia was equal between combination therapy and monotherapy with either class. A subgroup analysis focussing on Asian participants noted higher HbA1c reduction compared to non-Asian participants.

Extra-glycemic benefits:

Cardiovascular outcomes: DPP4i have shown no cardiovascular benefits in trials, except Saxagliptin which showed increased risk of heart failure hospitalization. SGT2i, on the other hand, has shown class benefit in reducing risk of heart failure hospitalization. However, it is important to note that Empagliflozin has shown benefits in cardiovascular outcomes even after exclusion of heart failure hospitalization parameter, while dapagliflozin has not. Thus, it is important to note that the benefit of dapagliflozin in composite cardiovascular outcomes is influenced by its benefit in reducing heart failure hospitalizations alone.

Renal outcomes: While DPP4i like Linagliptin have been found to be safe in end-stage renal disease (ESRD), DPP4i as a class offer minor renoprotective benefits in reducing albuminuria with inconsistent effects noted on progression to ESRD. SGLT2i, on the other hand, has shown class benefit in reduction of albuminuria and progression to ESRD, although the glycemic benefits are reduced at eGFR <60 ml/min/1.73m^2 and, are negligible at eGFR<30 ml/min/1.73m^2. It is important to note that eGFR reduction of 3-6 ml/min/1.73m^2 may be noted with SGLT2i initiation, due to attenuation of glomerular hyperfiltration associated with diabetic kidney disease.

Weight: DPP4i is weight neutral, while SGLT2i leads to weight loss averaging 2-3kg. Thus, both are good options for patients averse to weight gain.

Metabolic dysfunction-associated steatotic liver disease (MASLD): DPP4i are predominantly safe but offer no additive benefits. SGLT2i have shown benefits in reduction of hepatic steatosis parameters too.

Safety: Both the drug classes have very minimal hypoglycemia risk unless used alongwith other drug classes. DPP4i have predominantly gastrointestinal and flu-like side-effects, while SGLT2i may predispose the patient for ketosis and genital mycotic infections. Since the side-effect profiles of both drug classes differ significantly, there is no increased risk on combination therapy compared to individual therapy.

CONCLUSION

Based on the above evidence, we would like to conclude saying that DPP4i and SGLT2i are excellent agents for glycemic control. However, which agent to choose first would vary based on the patient profile. Being partners in glycemic control, combination therapy provides cardiorenal and extra-glycemic benefits in addition to marginally better glycemic control.

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Chapter 22

Oral GLP1 Agonists: A Game Changer

Chandan Sarmah

INTRODUCTION

Oral GLP-1 agonists, particularly semaglutide (Rybelsus) and the emerging pipeline of non-peptide alternatives like orforglipron, represent a pivotal advancement in managing type 2 diabetes and obesity. Historically, the GLP-1 receptor agonist (GLP-1 RA) class of medications required subcutaneous injections, which posed a significant barrier to adherence for many patients. The development of an oral formulation, a "peptide in a pill," addresses this core challenge, promising to transform therapeutic paradigms across the metabolic health landscape.

THE CHALLENGE OF ORAL DELIVERY: A SCIENTIFIC TRIUMPH

For decades, the oral delivery of peptide-based drugs like GLP-1 RAs was considered impossible due to their poor stability in the gastrointestinal (GI) tract and low permeability across the intestinal lining. The harsh, acidic environment of the stomach and the rapid enzymatic degradation posed formidable hurdles. Novo Nordisk overcame this challenge with the development of oral semaglutide by co-formulating the peptide with an absorption enhancer, sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC).

SNAC works by creating a transient, localized increase in the stomach's pH and protecting the semaglutide molecule from digestive enzymes. This facilitates the transcellular absorption of semaglutide across the gastric epithelial surface and into the bloodstream. While this innovation requires a specific administration protocol—taking the tablet on an empty stomach with a small amount of water, and waiting at least 30 minutes before eating—it was the first successful instance of oral peptide drug delivery.

CLINICAL EFFICACY: COMPARABLE TO INJECTABLES

Extensive clinical trial programs, such as the PIONEER and STEP studies, have demonstrated that oral GLP-1 agonists offer compelling efficacy in managing both type 2 diabetes and obesity.

- **For type 2 diabetes:** In the PIONEER trials, oral semaglutide demonstrated superior reductions in glycated hemoglobin (HbA1c) and body weight compared to other standard-of-care oral medications, like sitagliptin (a DPP-4 inhibitor) and empagliflozin (an SGLT2 inhibitor). In a head-to-head study (PIONEER 4), oral semaglutide 14 mg once daily showed non-inferior HbA1c reduction and superior weight loss compared to liraglutide 1.8 mg once daily injection. The most common side effects were mild-to-moderate and transient gastrointestinal issues.
- **For obesity:** Oral semaglutide has shown promising weight loss results, with higher doses (25 mg and 50 mg) achieving weight reductions similar to those seen with the injectable formulation (Wegovy). Higher

doses are associated with a greater reduction in body weight and HbA1c, while maintaining a safety profile consistent with the GLP-1 RA class.

- **Cardiovascular and renal benefits:** Like their injectable counterparts, oral GLP-1 agonists show cardiovascular safety and may offer protective benefits for the heart and kidneys. The SOUL cardiovascular outcomes trial for oral semaglutide has confirmed a significant reduction in major adverse cardiovascular events (MACE).

The "game-changing" impact on patients and prescribers

The shift from injectable to oral GLP-1 agonists fundamentally alters the treatment landscape in several key ways:

Improved patient adherence and psychological acceptance

Fear of needles (needle phobia) is a common barrier to treatment adherence and initiation for many individuals. The availability of an effective oral option, a form of medication that is familiar and universally accepted, removes this psychological and practical hurdle. For patients hesitant to self-inject, an oral GLP-1 agonist can be the deciding factor in starting and continuing a highly effective therapy.

Broader reach in primary care

Injectable therapies have traditionally been prescribed more cautiously, often requiring specialist supervision. The convenience of an oral tablet allows general practitioners and other primary care physicians to more readily initiate and manage GLP-1 RA therapy for appropriate patients. This broadens access and ensures more people can benefit from these potent medications earlier in their disease progression.

Enhanced scalability

From a public health and logistical perspective, oral medications are more scalable and easier to manage. They simplify storage, distribution, and administration, making them more adaptable for large-scale health programs and for use in settings with limited resources.

LIMITATIONS AND FUTURE DEVELOPMENTS

Despite the significant breakthroughs, oral GLP-1 agonists are not without limitations.

- **Dosing requirements:** The strict fasting and water-volume requirements of current oral formulations like Rybelsus can still be challenging for some patients to adhere to consistently, potentially impacting long-term compliance.
- **Adverse events:** Like the injectable versions, oral GLP-1 RAs are associated with gastrointestinal side effects, such as nausea, diarrhea, and vomiting, especially during dose escalation.
- **Cost:** Oral GLP-1 agonists remain expensive, which can be a significant barrier to accessibility, particularly for obesity treatment where insurance coverage may be limited.
- **Bioavailability:** The low bioavailability of current oral peptide formulations necessitates higher doses of the active ingredient compared to injections, which may increase manufacturing costs.

Future innovations are already addressing these challenges:

- **Next-generation oral peptides:** Pharmaceutical companies are working on developing oral peptide drugs with improved bioavailability and potentially longer half-lives, which could lead to once-weekly oral options.
- **Small-molecule agonists:** Oral, non-peptide GLP-1 RAs, such as orforglipron, offer a different approach that avoids the GI

absorption challenges of peptides. In clinical trials, orforglipron has shown high efficacy for weight loss, and its smaller, non-peptide structure may simplify administration protocols and production.

- **Combination therapies:** Next-generation medications are exploring dual and triple agonists that target GLP-1 receptors alongside other gut hormone receptors like GIP and glucagon. These multi-target therapies, like tirzepatide (a GIP/GLP-1 RA), could offer even greater efficacy for weight loss and cardiometabolic improvements.

CONCLUSION

The arrival of oral GLP-1 agonists represents a landmark moment in the treatment of metabolic disease. By overcoming a long-standing scientific barrier, these oral therapies have democratized access to a powerful class of medications, promising to improve patient adherence and broaden the reach of these treatments. While initial formulations still have some administration requirements and side effects, the pipeline of next-generation oral peptides and small-molecule agonists signals a future with more convenient and effective options. As research continues to expand the therapeutic indications and refine the delivery methods, oral GLP-1 agonists are set to solidify their position as a cornerstone of metabolic care, fundamentally redefining how type 2 diabetes and obesity are managed worldwide.

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Chapter 23

Are PPAR Agonists still useful in Diabetes?

Pranab Kumar Biswas

INTRODUCTION

Diabetes is a complex metabolic disorder whose prevalence is increasing globally and has become a major health problem. Currently, diabetes represents a challenging scenario and a global health crisis. India lies at the epicentre. According to the *Diabetes Atlas* published by the International Diabetes Federation in 2024, an estimated 589 million adults aged between 20–79 years (approximately 1 in 9 persons), were living with diabetes. This number is projected to soar to 853 million by 2050. This escalating crisis is driven largely by the rise in Type 2 Diabetes Mellitus (T2DM). The journey of PPAR agonists in diabetes treatment has been marked by both successes and setbacks. Initial enthusiasm for the potent glucose-lowering effects of TZDs was tempered by safety concerns.

PEROXISOME PROLIFERATOR - ACTIVATED RECEPTOR (PPAR) PHYSIOLOGY

Peroxisome proliferator - activated receptor (PPAR) are nuclear receptor proteins that act as, transcription factors, regulating genes involved in various physiological functions. There are three PPAR isoforms with distinct distributions and functions:

- PPARα (alpha): Highly expressed in liver, heart, and skeletal muscle. Activation boosts fatty acid oxidation and lowers triglycerides.
- PPARγ (gamma): Found mainly in adipose tissue (and also in liver and muscle). It regulates adipogenesis, lipid storage, and insulin sensitivity and thereby lower blood sugar level.
- PPARδ/β (delta): Expressed in brain, adipose tissue, and skin, involved in fatty acid oxidation. Research is going on with this isoform for its roles in metabolic syndrome.

PPAR agonists form a heterodimer with retinoid X receptor (RXR). Upon ligand binding, a complex of PPAR–RXR formed. It leads to conformational changes. This complex binds with a region on the gene, which is called as Peroxisome Proliferator Response Elements (PPREs) in DNA. This further leads to gene transcription. Transcription further leads to metabolic effects. PPARγ agonists are also called as Thiazolidinediones (TZDs). TZDs are powerful selective agonists of PPARγ receptors. TZD enhance insulin sensitivity in adipose tissue, liver, and muscle.

TZDs promote the following functions:

1. Promote differentiation of preadipocytes to mature adipocytes, which store free fatty acids (FFA). TZD lower circulating levels of FFA & reduce insulin resistance.
2. TZD modulate adipokines production. TZD increase adiponectin which leads to increased insulin sensitivity level. TZD reduce inflammatory cytokines eg, TNF-α.
3. TZD Increase expression of Insulin Receptor

Substrate2 (IRS-2), an intracellular component, essential for insulin and Insulin-Like Growth Factor (IGF-1) signalling.

TZDs reduce Plasminogen Activator Inhibitor-1(PAI-1) and C-reactive protein (CRP). It indicates, TZD reduce markers of inflammation and thrombosis

CLINICAL EFFECTS OF TZDs AND ROLE IN MANAGEMENT

It reduces HbA1c and also improves lipid profiles (increase HDL, shift small dense LDL to less atherogenic forms), and provide durable glycemic control. Hypoglycaemia risk is low with TZD. Lobeglitazone is a newer TZD introduced in India. Fibrates (fenofibrate, gemfibrozil, bezafibrate) activate PPARα to enhance fatty acid oxidation, reduce VLDL (lowering triglycerides) and raise HDL. In type 2 diabetes, where dyslipidaemia is common (high triglycerides, low HDL, dense LDL), fibrates reduce cardiovascular risk and may modestly lower glucose.

Dual / Mixed PPAR Agonists & Partial Agonists

- Dual PPARα/γ agonists are also known as "glitazars". Glitazars lower hyperglycaemia and diabetic dyslipidaemia (e.g., Saroglitazar, now approved in India for diabetic dyslipidaemia).
- PPARγ/δ agonists are being investigated to enhance insulin sensitivity without causing weight gain. Weight gain is seen with PPARγ molecules.
- Selective partial PPARγ agonists (SPPARMs) are now being investigated. It is expected that, in future, we will be able to develop improved SPPARM molecules. Research is going to retain beneficial effects but to reduce adverse effects, like edema and weight gain.
- Telmisartan (an angiotensin receptor blocker) & it has minor PPARγ partial agonist activity leading to minor metabolic benefits.

PPAR-alpha agonists were first introduced in 1960 for treatment of dyslipidaemia eg Fibrates. Fibrates are synthetic PPAR-alpha agonists. A PPAR-alpha agonist is a type of molecule that activates the Peroxisome Proliferator-Activated Receptor alpha (PPAR-α), which plays a role in regulation of lipid metabolism and inflammatory responses.

Currently, In India, Pioglitazone and Lobeglitazone are available for treatment of T2DM. They are also termed as Ligands. Ligands is a molecule that binds to a specific receptor to transmit signals inside or between cells. When a ligand binds to its receptor, it triggers signals intracellular. Signal transduction leads to activation of specific gene. Subsequently gene expression takes place. Gene expression leads to its response. Cellular response. Ligands may be Endogenous (naturally occurring) or Exogenous (synthetic, such as drugs eg TZD).

During mid-1990s, synthetic Thiazolidinediones (TZD) (PPARγ agonist) were introduced for treatment of T2DM. Examples of PPARγ agonists are Troglitazone, Rosiglitazone, Pioglitazone and Lobeglitazone. Troglitazone was soon banned for therapeutic purpose for its hepatotoxicity. Later, Rosiglitazone was also withdrawn for its adverse cardiac effect.

Pharmacological treatment of type 2 diabetes is complex one. There is wide range of molecules are available for treatment ofT2DM. They are oral and injectable molecules. Among the oral medications, Peroxisome Proliferator-Activated Receptor (PPAR) agonists still play an important role. Different types of PPAR agonists are available for therapeutic purpose. Leading guidelines also included PPAR Agonists for treatment of Type 2 Diabetes Mellitus.

CONCLUSION

The drive of PPAR agonists in diabetes treatment has been marked by both successes and impediments. PPARγ agonists are important therapeutic agents in the management of T2DM, especially with significant insulin resistance. TZDs effectively

lowers insulin resistance and also of help in hepatic steatosis. Hypoglycaemia risk is minimal with TZDs. However, due to side effects of TZD, their use must be carefully considered. Ongoing research, aims to develop safer and more effective PPAR modulators (dual, pan, partial, and tissue-selective) with improved benefit profiles. These next-generation PPAR Agonists may enable personalized management of diabetes and its metabolic complications. PPAR Agonists are cheaper molecules. Cost effective treatment option of T2DM is relevant in our country. In conclusion, PPAR agonists are still relevant in Type 2 Diabetes management. Future advances in this field hold promise for improved treatment in diabetes.

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Section 08

Section Editor : **Pranab K Biswas**

Therapeutics: Insulin

Chapter 24

Knowledge and Standard Practice of Insulin Delivery in Patients with Diabetes

Jayanta Kumar Panda

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is a complex disease that affects multiple organ systems and is associated with significant morbidity and mortality worldwide. According to the International Diabetes Federation (IDF), over 537 million adults were living with diabetes in 2021, and this number is projected to rise to 783 million by 2045. Insulin therapy remains the cornerstone of treatment for individuals with Type 1 diabetes, where absolute insulin deficiency is present. It is also increasingly required in patients with Type 2 diabetes, particularly as the disease progresses and pancreatic β-cell function declines. Over the past century, significant advances have been made in insulin formulations and delivery devices, including the development of recombinant human insulin, insulin analogs with improved pharmacokinetic profiles, and sophisticated delivery systems such as insulin pens and pumps. Despite these advancements, several challenges remain, including ensuring accurate dosing, maintaining adherence to therapy, managing the risk of hypoglycemia, and addressing patient barriers such as fear of injections and limited access to resources.

In addition, modern diabetes management increasingly emphasizes individualized care, integrating patient education, lifestyle interventions, and technological tools such as continuous glucose monitoring and automated insulin delivery systems. Understanding current insulin delivery methods, standard practices, and emerging technologies is therefore critical for healthcare providers, educators, and researchers. Effective insulin therapy not only improves glycemic control but also reduces the risk of complications, enhances patient adherence, and ultimately contributes to a better quality of life for individuals living with diabetes.

TYPES OF INSULIN DELIVERY METHODS

1. Insulin Syringes

Insulin syringes remain widely used in many regions, particularly in low-resource settings, due to their affordability, availability, and simplicity. Despite being considered traditional, syringes require proper technique to ensure safe and effective administration.

Key considerations for syringe use include:

- Always use sterile, single-use syringes to prevent infection.
- Select the appropriate needle length (typically 4–8 mm) based on patient body mass index (BMI) and subcutaneous tissue thickness.
- Administer injections subcutaneously at a 90° angle; in lean individuals, a pinch of skin may be required.
- Systematically rotate injection sites to prevent lipohypertrophy and maintain consistent insulin absorption.

While syringes remain effective, they are less

convenient than modern devices and are associated with a higher risk of dosing errors, decreased patient adherence, and social discomfort due to their less discreet nature. Nevertheless, for patients in low-resource settings, syringes continue to be a reliable and cost-effective method of insulin delivery.

2. Insulin Pens

Insulin pens have become the preferred method of insulin administration in many clinical settings due to their convenience, accuracy, and ability to improve adherence. Pens are available in both pre-filled and refillable formats and allow for more precise dosing with minimal preparation time.

Advantages include:

- Reduced dosing errors compared to syringes.
- Portability and ease of use in public settings, enhancing patient discretion.
- Integration with "smart" technology: Some pens track dosing history, provide reminders, and can interface with mobile applications or CGM data to optimize therapy.

Clinical studies consistently demonstrate that insulin pens improve glycemic control, enhance patient satisfaction, and support better adherence compared to traditional syringe use. They are particularly beneficial for elderly patients, those with visual impairment, or patients with limited dexterity.

3. Insulin Pumps

Insulin pumps, also known as Continuous Subcutaneous Insulin Infusion (CSII) devices, deliver rapid-acting insulin continuously to mimic physiological insulin secretion.

Key features:

- Programmable basal rates to match circadian insulin needs.
- Bolus dosing for meals and correction of hyperglycemia.
- Integration with continuous glucose monitoring (CGM) to adjust doses dynamically.

CSII therapy has been shown to improve glycemic control, increase time-in-range, and reduce the incidence of severe hypoglycemia. Advanced hybrid closed-loop systems, which combine insulin pumps with CGMs and automated algorithms, provide a semi-physiologic insulin delivery pattern that reduces patient burden and improves overall metabolic control.

4. Automated Insulin Delivery (AID) Systems

Automated Insulin Delivery systems represent the latest innovation in diabetes management. These devices integrate insulin pumps with CGMs and intelligent algorithms to adjust insulin delivery in real time. The goal of AID systems is to emulate the function of a healthy pancreas, delivering insulin dynamically in response to fluctuating glucose levels.

Clinical benefits include:

- Increased "time-in-range" and improved glycemic control.
- Reduction in hypoglycemia episodes, particularly nocturnal events.
- Improved patient satisfaction and quality of life due to reduced manual interventions.

5. Inhaled and Alternative Delivery Methods

Inhaled insulin offers a non-invasive alternative to subcutaneous injections, providing rapid absorption and convenience for mealtime insulin delivery. While effective, its use is limited by factors such as the need for baseline pulmonary function testing, higher cost, and variable patient acceptance.

Other non-invasive delivery methods under investigation include:

- **Transdermal patches:** Slow, sustained insulin absorption through the skin.
- **Oral insulin formulations:** Designed to improve patient comfort and adherence; bioavailability remains a challenge.

- **Microneedle arrays:** Minimally invasive devices delivering insulin through the skin with reduced pain and enhanced compliance.

These emerging technologies aim to reduce injection-related barriers, improve adherence, and enhance the overall patient experience while maintaining effective glycemic control.

STANDARD PRACTICES IN INSULIN ADMINISTRATION

Optimal insulin therapy not only depends on the correct formulation and device but also on meticulous attention to injection technique, site selection, and dose adjustment. Proper administration is crucial for achieving consistent glycemic control, preventing complications, and enhancing patient adherence.

Injection Site Selection

Selecting the appropriate injection site is a key determinant of insulin absorption and glycemic stability. The pharmacokinetics of insulin vary depending on the site of administration, depth of injection, and local tissue characteristics. Commonly used sites include:

- **Abdomen:** The most commonly preferred site due to the fastest and most consistent absorption. Ideal for rapid-acting insulin administered before meals. The periumbilical region should be used with a minimum distance of 2 cm from the navel.
- **Thighs (anterior and lateral aspects):** Absorption is slower than the abdomen, making it suitable for basal insulin administration. Avoid injecting too close to the knee to minimize variability.
- **Upper arms (posterolateral aspect):** Moderate absorption; often convenient for self-injection in patients with limited mobility.
- **Buttocks (upper outer quadrant):** Slowest absorption; ideal for long-acting insulin. This site is often preferred for patients requiring predictable basal insulin coverage.

Site rotation is essential to prevent lipohypertrophy, scarring, or local inflammation, which can alter insulin absorption and lead to erratic glucose levels. A common strategy is to divide each site into quadrants or regions and rotate injections sequentially within each quadrant over days or weeks.

Injection Technique

Proper injection technique ensures that insulin is delivered into the subcutaneous tissue, avoiding intramuscular administration, which can cause unpredictable absorption and hypoglycemia. Key recommendations include:

- Clean the skin with mild antiseptic **only if visibly soiled**, as routine alcohol swabbing is not always necessary and may cause skin irritation.
- Use the correct needle length (typically 4–6 mm for most adults) and insert at a **90° angle**; shorter needles reduce the risk of intramuscular injection.
- For lean individuals or children, a gentle **pinch of skin** is recommended to lift the subcutaneous layer away from underlying muscle.
- Avoid injecting into **scarred, inflamed, bruised, or lipohypertrophic areas**, as these can impair insulin absorption.
- After injection, leave the needle in place for 5–10 seconds to allow complete insulin delivery and reduce leakage.

MONITORING AND DOSE ADJUSTMENT

Frequent monitoring is the cornerstone of effective insulin therapy. Regular glucose measurement allows clinicians and patients to make informed adjustments to insulin doses, preventing both hyperglycemia and hypoglycemia:

- **Self-Monitoring of Blood Glucose (SMBG):** Recommended 3–6 times per day for patients on intensive insulin therapy, including pre-meal, post-meal, and bedtime checks.

- **Continuous Glucose Monitoring (CGM):** Provides real-time glucose readings and trend analysis, enabling proactive management of hyperglycemia and hypoglycemia. CGM data can guide basal rate adjustments, correction doses, and lifestyle interventions.
- **Dose Titration:** Insulin doses should be titrated based on glucose patterns, carbohydrate intake, activity level, and patient-specific targets. Adjustments should be gradual and evidence-based to reduce the risk of hypoglycemia.
- **Hypoglycemia Management:** Patients and caregivers should receive structured education on recognizing symptoms, correcting low blood glucose, and preventing recurrent episodes.

CHALLENGES IN INSULIN THERAPY

1. Adherence

Non-adherence is a major barrier, influenced by fear of injections, regimen complexity, and lack of education. Pen devices and digital reminders improve adherence and glycemic outcomes.

2. Hypoglycemia

Intensive insulin therapy increases hypoglycemia risk. Education, CGM, and AID systems help mitigate this risk.

3. Cost and Accessibility

Insulin and modern devices can be prohibitively expensive in low-resource settings. Efforts to improve affordability include biosimilar insulin production and government subsidy programs.

4. Healthcare Infrastructure

Limited access to trained healthcare providers and cold-chain logistics in rural areas can impede proper insulin administration.

CONCLUSION

Insulin delivery has evolved from crude animal extracts and glass syringes to sophisticated pens, pumps, and automated systems. Understanding standard practices, site rotation, dosing strategies, and emerging technologies is crucial for healthcare professionals managing diabetes. Optimizing insulin therapy requires a patient-centred approach, combining accurate delivery, adherence support, and continuous monitoring to reduce complications and improve quality of life. Continued research and innovation will ensure insulin therapy and practice of insulin delivery remains effective, safe, and accessible worldwide.

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Chapter 25

Promises with Concentrated Insulin

Swapnav Borthakur

INTRODUCTION

Type 2 diabetes mellitus is becoming more common worldwide, coinciding with the obesity and metabolic syndrome epidemics. As the severity of insulin resistance increases, more patients need high insulin dosages to attain ideal glycemic control. Because of their high injection volumes, inconsistent absorption, and poor adherence, conventional U-100 insulin formulations frequently become unfeasible for people who require more than 200 units daily. Because they provide comparable glycemic control in smaller volumes, concentrated insulins—formulations with more insulin units per milliliter (U-200, U-300, and U-500)—represent a significant advancement. These preparations lower the risk of hypoglycemia while improving adherence, patient comfort, and absorption kinetics.

Insulin, which was discovered in 1922, has changed the treatment of diabetes mellitus from a deadly illness to a chronic condition that can be controlled. Its pharmacokinetic and pharmacodynamic qualities have been improved over time by a number of formulation advancements, starting with animal-derived insulin and progressing to recombinant human insulin and, ultimately, insulin analogues. Notwithstanding these developments, the current difficulty is in treating patients with insulin resistance brought on by obesity, who frequently need daily dosages of more than 200 units. Standard U 100 insulin can be difficult to administer in such high doses, requiring numerous injections and large injection volumes that impair adherence, consistency, and absorption. By boosting insulin unit density while maintaining molecular identity and biological potency, concentrated insulin formulations were created to address these problems. They offer a more physiologically predictable absorption profile and allow for reduced injection volume, enhanced patient satisfaction, and improved compliance— features that are particularly valuable in patients with severe insulin resistance.

FORMULATION SCIENCE

Concentrated insulins are modified pharmaceutical formulations intended to contain more insulin units per milliliter without compromising biological activity; they are not novel molecular entities. Recombinant DNA technology is used to produce them in host systems of either Saccharomyces cerevisiae or Escherichia coli. Excipients like zinc ions, glycerol, phenol, and isotonic buffers are used to stabilize the insulin molecule in order to preserve its solubility and stability at high concentrations. While the molecular structure of rapid-acting concentrated analogues like U 200 lispro is the same as that of U 100 lispro, the injection volume is cut in half, improving absorption uniformity and lowering injection-site variability. Long-acting analogues such as U 300 glargine and U 200 degludec are designed to form stable micro precipitates in subcutaneous tissue, creating smaller and denser depots that dissolve slowly, thereby prolonging duration of action and flattening the pharmacodynamic curve. U 500 regular insulin, though older, remains valuable due to its unique pharmacokinetic profile that combines basal and prandial properties in a single formulation.

HISTORICAL TIMELINE OF CONCENTRATED INSULIN DEVELOPMENT

Year/Period	Milestone	Key Details & Significance
1920s – 1950s	**Early Insulin Concentrations (U-20**	Multiple insulin strengths were available, leading to frequent dosing errors and variable glycemic control.
1950s	**Introduction of U-500 Regular Insulin**	Eli Lilly developed U-500 regular insulin for patients with severe insulin resistance who required large daily doses.
1973	**FDA Standardizes Insulin**	The U.S. FDA mandated U-100 as the universal standard to minimize dosing errors and improve
1980s– 1990s	**Advances in Recombinant Insulin Technology**	Introduction of human recombinant insulin laid the foundation for stable and predictable analogues.
Early 2000s	**Emergence of Insulin Analogues**	Development of rapid- and long-acting analogues improved pharmacokinetics and patient adherence.
2015– 2017	**Launch of Modern Concentrated Insulin Analogues**	**U-300 Glargine (Toujeo®)** – prolonged duration and smoother profile **U-200 Degludec (Tresiba®)** – ultra-long basal action **U-200 Lispro (Humalog®)** – concentrated rapid- acting option
2020s– Present	**Integration with Automated Insulin Delivery (AID) Systems**	Research now focuses on combining concentrated insulins with AID and hybrid closed-loop systems, advancing precision diabetes management.

PHARMACOKINETICS AND CLINICAL PROFILES

Formulation	Concentration	Type	Duration/ Action	Clinical Advantage
U-200 Lispro	200 U/mL	Rapid-acting	3–4 h	Same onset as U-100; smaller volume → better absorption &
U-300 Glargine	300 U/mL	Long-acting basal	30–36 h	Flatter, prolonged action; reduced nocturnal hypoglycemia
U-200 Degludec	200 U/mL	Ultra-long basal	>42 h	Ultra-flat curve; lowest hypoglycemia risk; flexible dosing
U-500 Regular	500 U/mL	Regular insulin	Up to 24 h	Dual basal-bolus; fewer injections in insulin-resistant patients

CLINICAL EVIDENCE

- **U-300 Glargine (EDITION Trials):** Similar HbA1c to U-100; 20–30% reduction in nocturnal hypoglycemia.
- **U-200 Degludec (SWITCH, DEVOTE Trials):** Ultra-long half-life; 40% reduction in severe hypoglycemia; cardiovascular safety confirmed.
- **U-200 Lispro:** Bioequivalent to U-100; convenience for high pre-meal doses.
- **U-500 Regular:** Improves control with fewer injections for insulin-resistant patients.
- **Emerging Research:** U-200 Lispro and U-500 Aspart show promise for automated insulin delivery systems (2024–2025).

ADVANTAGES

1. Reduced injection volume → less discomfort, better acceptance.
2. Improved absorption & pharmacodynamics → predictable plasma insulin.
3. Lower hypoglycemia risk (especially U-300 Glargine & U-200 Degludec).
4. Enhanced adherence → fewer injections, compact devices.
5. Compatible with AID and insulin pumps.
6. Reduced day-to-day glucose variability.

RESTRICTIONS

1. Dosing errors: Because concentrated units are high-risk, patient education is essential.
2. Cost and accessibility: A little more expensive, with less insurance coverage in areas with limited resources.
3. Compatibility of devices: Not all pumps or pens can use concentrated insulin.
4. Pregnancy and pediatric data are limited; further research is required.

PROSPECTS FOR THE FUTURE

Diabetes care is changing quickly in the direction of personalized treatment and automation. Concentrated insulins are ideally suited for incorporation into automated insulin delivery systems of the future due to their predictable pharmacokinetics and smaller injection volume.

Algorithmic recalibration to account for fluctuating insulin concentrations while preserving closed loop accuracy is the subject of ongoing research. For patients who need high daily insulin dosages, new formulations like U 500 Aspart and ultra-concentrated degludec analogs may make compact pump cartridges and longer wear times possible. Additionally, concentrated insulins are anticipated to be crucial in optimizing automated delivery systems by decreasing refill frequency and improving dosing accuracy as machine learning and artificial intelligence continue to progress in glucose prediction.

CONCLUSION

Formulations of concentrated insulin are a significant development in the treatment of diabetes today. They overcome significant obstacles to adherence, comfort, and safety for people with insulin resistance by providing the same glycemic control in smaller injection volumes. These preparations, which range from the early release of U 500 regular insulin to the current U 300 glargine and U 200 degludec, represent the continuous improvement of insulin therapy in the direction of increased convenience and physiological stability. Concentrated insulins have the potential to revolutionize diabetes treatment by facilitating customized, low volume, and extremely stable insulin replacement regimens as their integration into automated insulin delivery platforms progresses. Their creation represents a step toward genuinely patient-centered diabetes care as well as a pharmacological advancement.

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Chapter 26

The Need of SMART Insulin- Once a week vs Glucose sensitive insulin

Samiran Das

INTRODUCTION

Modern diabetes therapy strives for a paradigm shift from "injection burden and error-prone dosing" toward "minimal intervention with maximal safety and efficacy." Classical basal and bolus insulins, despite advances in analog design and delivery systems, still pose adherence challenges and expose patients to hypo- and hyperglycaemia. Smart insulins—either with extended duration or intrinsic glucose sensitivity—seek to address these hurdles. Smart insulin represents one of the most promising horizons for diabetes management, aiming to simplify treatment, reduce hypoglycemia risk, and closely mimic physiological insulin secretion. Currently, two of the most innovative directions are once-weekly insulins and glucose-sensitive (or glucose-responsive) insulins. This review emphasises the need, progress, and comparative promise of these two classes of insulin formulations, drawing from the most recent literature and clinical developments.

RATIONALE FOR SMART INSULIN

The main limitations of current insulin therapies include:

- Multiple daily injections leading to poor adherence, especially in populations with psychological resistance, pediatric, or elderly cohorts.
- High risk of hypoglycemia due to overcorrection or mismatched insulin timing.
- Inability to precisely mimic physiologic insulin secretion in response to dynamically changing glucose levels.
- Increased clinical inertia and dosing confusion in complex regimens.
- Smart insulin solutions are designed to address these core needs.

ONCE-WEEKLY INSULINS: INNOVATIONS, EFFICACY, AND NEEDS

Mechanism and Clinical Rationale

Once-weekly insulins (such as icodec, efsitora alfa, and others) are engineered for ultra-long duration, providing stable basal insulin coverage with only one injection per week. This pharmacokinetic advantage is achieved by modifications that slow absorption, reduce clearance, and enable depot formation.

Evidence from Clinical Trials

- Efficacy for glycemic control in type 2 diabetes is comparable—or in some trials superior—to once-daily basal analogs, with similar reductions in HbA1c and time-in-range metrics.
- Hypoglycemia rates are non-inferior to standard basal insulins in most populations, though concerns remain for those with erratic glucose dynamics.
- Real-world and trial evidence points to markedly improved treatment persistence

and adherence, especially for individuals deterred by daily injections.

- Safety signals—namely injection site reactions or antibody development—are minimal and manageable within trial follow-up durations.

Practical Considerations

- Dosing transitions from daily to weekly require structured algorithms (e.g., loading doses, titration schedules), which may hinder universal adoption without robust education.
- Missed dose management, surgical or acute illness adjustments, and transition protocols remain areas of ongoing study.
- Combination with weekly GLP-1 agonists (such as the IcoSema regimen) shows potential for comprehensive metabolic control with just one or two weekly injections.

Limitations

- In type 1 diabetes, once-weekly insulins may not fully match rapid shifts in insulin need, resulting in higher hypoglycemia risk or lesser treatment satisfaction—indicative of an incomplete physiological match.
- Reduced flexibility could be problematic in populations with highly variable insulin requirements.

GLUCOSE-SENSITIVE (GLUCOSE-RESPONSIVE) INSULINS: MECHANISM AND PROMISE

Mechanistic Foundations

Glucose-sensitive insulins are bioengineered to adjust their activity or release rate in direct response to circulating glucose concentrations, ideally approximating endogenous beta-cell secretion. Approaches include:

- Insulin conjugates with glucose-binding macrocycles, reversible switches, or glucose-sensitive carrier matrices.
- Synthetic patches, depots, or nanoparticles incorporating glucose oxidase or other glucose-responsive elements that modulate insulin release.

Preclinical and Clinical Evidence

- Molecules such as NNC2215 have demonstrated reversible affinity changes for the insulin receptor in response to glucose, leading to increased bioactivity during hyperglycaemia and reduced action during euglycemia/hypoglycaemia.
- Animal studies consistently show hypoglycemia protection without forfeiting hyperglycaemia correction—addressing the main risk in intensive insulin therapy.
- Multiple designs (patches, injectable depots, implantable devices) have been tested, some reaching early phase clinical assessment.

Clinical Translation Barriers

- Biological complexity: Engineering an insulin that exhibits swift, robust, and truly physiological glucose sensitivity has proven difficult, with full reversibility and appropriate kinetics still under development.
- Variability in subcutaneous tissue and unpredictable absorption under different conditions (exercise, temperature, tissue health) complicates real-life performance.
- Although animal data is promising, human trials remain limited and primarily early phase—so real-world glycemic outcomes and safety profiles await further validation.

Comparative Analysis

Aspect	Once-weekly Insulin	Glucose-Sensitive Insulin
Mechanism	Ultra-long acting, stable depot	Dynamic release/activation upon high glucose
Glycaemic Control	Effective for basal needs	Potential for both basal and rapid correction
Hypoglycaemia Risk |	Comparable to daily basal, but not eliminated	Expected to minimize hypoglycaemia markedly
Dosing Convenience	1/7th frequency; improved adherence	Ideally eliminates manual dose timing
Flexibility	Reduced dose flexibility	Maximum physiological soundness (if fully realized)
Status	| Large trials (Phase 3/4); some approvals	Preclinical/early phase human trials
Limitations	Less suitable for volatile T1D; transition complexity	Scalability, speed of response, regulatory hurdles

THE CLINICAL NEED: WHY BOTH APPROACHES MATTER

- Adherence Simplification': Both approaches are crucial to address the psychological and practical burdens of lifelong diabetes management.'
- Physiological Mimicry': Glucose-sensitive insulin, if perfected, holds the promise of true closed-loop, "on-demand" insulin delivery—currently only partially emulated by advanced pump/CGM systems or hybrid closed-loop devices.'
- Individualization': The choice between therapies will depend on patient age, comorbidities, insulin requirement variability, capacity for self-management, and real-world risk of hypoglycaemia.

FUTURE PERSPECTIVES AND UNMET NEEDS

- Long-term safety and rare side effects for weekly insulins require ongoing large-cohort follow-up.
- Engineering challenges for glucose-sensitive insulin—ranging from consistent manufacturing, safety, tissue compatibility, and regulatory clarity—must be overcome for widespread usage.
- Combined smart therapies: The horizon may see co-formulated "ultra-long" and "glucose-sensitive" insulins, or hybrid systems leveraging depot insulin with feedback-responsive pumps or patches for optimal control.

CONCLUSION

The evolution of insulin therapy is reaching a new frontier with once-weekly and glucose-sensitive insulins. While once-weekly formulations already have demonstrated efficacy for reducing patient burden and improving adherence, glucose-sensitive insulins may eventually usher in an era of near-physiological glycemic control and freedom from hypoglycemia. Both are crucial advancements, with complementary and distinct applications in the smart insulin landscape.

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Chapter 27

Exploring Alternate Routes of Insulin Delivery

Uttam Kumar Nath
Naruttam Sonowal
Bhargab Protim Borah

INTRODUCTION

Alternate routes of insulin delivery have long been explored to overcome the limitations of traditional injections and to improve the quality of diabetes care. The discovery of insulin in 1921 by Banting, Best, and Macleod provided the first effective treatment for diabetes, initially administered through intravenous and intramuscular routes, which, although lifesaving, were associated with pain, variable absorption, and limited practicality [(1).] Over time, the subcutaneous route emerged as the standard method, offering greater convenience and more predictable absorption, yet challenges such as delayed onset of action, variability in glycemic control, and the psychological burden of repeated needle use persisted. These obstacles stimulated intensive research into innovative delivery systems, including oral, inhaled, transdermal, buccal, and implantable methods, each striving to replicate the physiological profile of endogenous insulin more closely [(2)]. In recent decades, despite major technological advances, modern therapy continues to face barriers such as inconsistent bioavailability, high costs, and restricted accessibility of newer formulations. The ongoing pursuit of alternate insulin delivery routes showing remarkable progress since the pioneering work of Banting and Best to optimize the care for people living with diabetes.

PHYSIOLOGICAL BASIS

The physiology and anatomy of the human skin play a critical role in the absorption and efficacy of alternate insulin delivery systems. Skin is a multi-layered organ consisting of the epidermis, dermis, and subcutaneous tissue, with thickness and vascularization varying by body site, age, and individual factors. The stratum corneum, the outermost layer of the epidermis, is the primary barrier to transdermal absorption, limiting passive diffusion of large peptide molecules like insulin. Beneath this layer, the dermis contains capillaries and lymphatics that can facilitate systemic uptake if permeability is enhanced through microneedles, iontophoresis, or chemical enhancers. Subcutaneous tissue, traditionally targeted for injections, provides slower absorption due to limited blood flow in some regions, creating variability in insulin pharmacokinetics. These anatomical and physiological constraints have driven the exploration of novel delivery routes, including transdermal patches, intradermal microinjections, and mucosal pathways, which exploit highly vascularized surfaces to mimic endogenous insulin kinetics.

ROUTES OF INSULIN DELIVERY

SUBCUTANEOUS ROUTE

Subcutaneous administration remains the most widely used route for insulin delivery in both type 1 and type 2 diabetes due to its relative ease, predictable absorption, and suitability for self-administration. The technique involves injecting insulin into the subcutaneous tissue, a layer of fat beneath the dermis, which allows slower absorption

than intramuscular or intravenous routes, thereby providing a more sustained effect. Commonly recommended injection sites include the abdomen, upper arms, anterior and lateral thighs, and the buttocks. Site rotation is critical to prevent lipohypertrophy, a localized thickening of subcutaneous tissue that can alter absorption and insulin action. Proper technique involves pinching the skin to avoid intramuscular injection, selecting the appropriate needle length, and injecting at a 90-degree angle for most adults, though shorter needles and 45-degree angles may be used in lean individuals or children.

Several factors influence the absorption of subcutaneously injected insulin, including local blood flow, temperature, physical activity, and the specific site of injection. Insulin injected into the abdomen tends to have the fastest absorption, followed by the arms, thighs, and buttocks. Exercise can increase blood flow to the site and accelerate absorption, while lipohypertrophy or scar tissue can reduce bioavailability. The pharmacokinetics of insulin also depends on the formulation, with rapid-acting analogues absorbed more quickly than long-acting basal formulations. Concentration variations such as U100, U200, and U300 are designed to provide flexibility in dosing and allow delivery of higher insulin units in smaller volumes, which can improve comfort and absorption consistency. Insulin formulations are either cloudy (suspensions, e.g., NPH) requiring mixing, or clear (solutions, e.g., rapid- and long-acting analogues). Subcutaneous injections can cause pain, bruising, infection, lipohypertrophy, and systemic hypoglycemia if absorption varies.

Various devices are available to facilitate subcutaneous insulin administration. Traditional vials and syringes remain widely used, particularly in resource-limited settings. Insulin pens, including disposable and reusable models, provide greater dosing accuracy, ease of use, and improved patient adherence. Pre-filled cartridges are available in many pen systems, allowing for flexible dosing of concentrated insulins such as U300 glargine, which is particularly useful in patients requiring high doses. Needle length selection, injection technique, and device choice are critical considerations in optimizing therapy and minimizing complications. Recent advances in pen technology include memory functions, dose counters, and connectivity features for digital tracking, further enhancing safety and adherence.

Overall, subcutaneous insulin administration remains the cornerstone of diabetes management. Its efficacy and safety depend on proper technique, careful site selection, awareness of absorption-modifying factors, and the appropriate choice of insulin formulation and delivery device. Understanding these aspects enables clinicians to optimize glycemic control while minimizing complications and improving patient satisfaction.

CONTINUOUS INSULIN DELIVERY SYSTEM

Continuous insulin delivery systems, encompassing closed-loop systems and bionic pancreas devices, represent significant advancements in diabetes management. These systems aim to automate insulin delivery by integrating real-time glucose monitoring with insulin pumps, thereby mimicking pancreatic function. Recent trials have demonstrated the efficacy of these systems in improving glycemic control. Study published in the *New England Journal of Medicine* in 2023 highlighted the benefits of closed-loop insulin delivery in young children with type 1 diabetes, showing improved glucose control and reduced hypoglycemia. Similarly, trial conducted in 2023 reported that fully automated closed-loop insulin delivery improved glucose control without increasing hypoglycemia in adults with type 2 diabetes.

The integration of artificial intelligence (AI) into these systems has further enhanced their capabilities.

AI algorithms analyse continuous glucose data to predict future glucose levels and adjust insulin delivery accordingly, leading to more precise and personalized diabetes management. A study in 2024 demonstrated that AI-driven closed-loop systems could effectively manage glucose levels in patients with type 2 diabetes, highlighting the potential of AI in expanding the applicability of these systems.

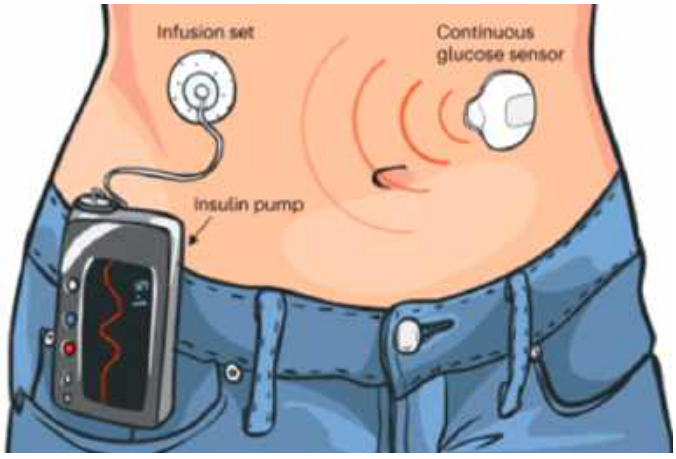

Fig. Close Loop Continuous Insulin delivery system

Continuous glucose monitoring (CGM) provide real-time glucose readings, allowing for timely adjustments in insulin delivery. American Diabetes Association (ADA) and the International Diabetes Federation (IDF) recommend the use of CGMs in conjunction with insulin therapy to improve glycemic control and reduce the risk of hypoglycemia, particularly in patients with type 1 diabetes. The National Institute for Health and Care Excellence (NICE) in the UK recommends hybrid closed-loop systems for adults with type 1 diabetes who have an HbA1c of 58 mmol/mol (7.5%) or higher, or who experience disabling hypoglycemia despite optimal management. Similarly, the ADA has acknowledged the benefits of automated insulin delivery systems in improving glycemic control and reducing the burden of diabetes management for both type 1 and type 2 diabetes.

These advancements in continuous insulin delivery systems, powered by AI and CGM technology, offer promising prospects for diabetes management. Ongoing research and development aim to refine these systems further, making them more accessible and effective for a broader range of patients, while metrics such as "time in range" and reduced hypoglycemic events are increasingly used as key outcome parameters.

INTRAVENOUS ROUTE

Intravenous insulin therapy is a cornerstone in the management of hyperglycemia in hospitalized patients, particularly in critical care settings. This method allows for rapid and precise control of blood glucose levels, which is crucial in acutely ill patients who may experience significant fluctuations due to stress, infection, or other factors. The ADA recommends initiating intravenous insulin therapy for persistent hyperglycemia (≥180 mg/dL) in critically ill patients, to reduce the risk of complications such as infections and improve overall outcomes. In non-critical care settings, the approach to insulin therapy is more individualized. The ADA suggests initiating insulin therapy for persistent hyperglycemia (≥180 mg/dL) in non-ICU patients, but the preferred regimen may vary. Intravenous insulin may still be considered in situations requiring rapid glucose control or when oral medications are not feasible.

Transitioning from intravenous to subcutaneous insulin requires careful planning. The timing of this transition depends on the patient's clinical status, ability to tolerate oral intake, and stability of glucose levels. Typically, subcutaneous insulin is initiated 1–2 hours before discontinuing the intravenous infusion to ensure continuous glycemic control. Close monitoring is essential during this period to prevent hyperglycemia or hypoglycaemia.

INTRAMUSCULAR ROUTE

Intramuscular insulin administration is rarely used due to its rapid and unpredictable absorption compared with subcutaneous or intravenous routes, increasing the risk of hypoglycemia. It may be considered in special situations where subcutaneous

absorption is unreliable, such as in patients with severe peripheral edema or marked dehydration, which compromise tissue perfusion. IM injections provide more consistent insulin delivery in these cases but require close blood glucose monitoring and careful clinical supervision. Due to pain, risk of muscle injury, and impracticality for repeated dosing, IM insulin is generally reserved for hospital or emergency settings rather than routine therapy.

INHALATIONAL ROUTE

Inhalational insulin presents a promising alternative to traditional subcutaneous insulin injections for diabetes management, offering rapid absorption through the lungs. The first marketed inhaled insulin, Exubera, was launched in 2006 but withdrawn due to poor sales. Currently, Afrezza is the only FDA-approved inhaled insulin, known for its ultra-rapid action, peaking within 12-15 minutes post-inhalation. Afrezza uses Technosphere technology to deliver insulin powder to alveoli for swift absorption, improving postprandial glycemic control in adults with type 1 and type 2 diabetes. INHALE-3 trial has demonstrate its efficacy and patient satisfaction, highlighting its role as a needle-free option for prandial insulin delivery. The ADA 2024 Standards of Care, inhaled insulin, such as Afrezza, is listed as an alternative option for mealtime insulin in adults with diabetes, provided there is no underlying lung disease or recent smoking history. The IDF and NICE guidelines also recognize inhaled insulin as a prandial insulin alternative for suitable patients.

ORAL INSULIN

Oral insulin aims to improve patient convenience and adherence by replacing injectable forms with a non-invasive route. It offers a physiologically appealing route by delivering insulin through the gut, potentially mimicking portal circulation. Challenges include degradation in the stomach and low intestinal absorption. Advances in nanoparticles and chemical modifications have improved bioavailability, and early trials such as ORMD-0801 show promise. Though, oral insulin is still investigational and not yet in clinical use ongoing research and trials suggest it could become a vital alternative in future diabetes management.

OTHER ROUTES

Buccal insulin offers a non-invasive route with rapid absorption through the oral mucosa. Trials like those involving Oral-lyn have shown comparable glycemic control to subcutaneous insulin in type 1 and type 2 diabetes patients, although bioavailability remains a challenge.

Rectal insulin has been studied in formulations like gels and suppositories with pharmacologic availability around 25-32%. Early trials demonstrated moderate glucose control, suggesting potential as an alternative delivery route.

Transdermal insulin delivery employs patches, microneedles, or jet injectors to bypass injections. Recent clinical trials indicate its effectiveness and safety, with some formulations maintaining stable blood glucose levels for up to 15 hours.

Fig: Insulin Jet injectors

Ocular insulin, delivered as eye drops or topical formulations, shows promise for corneal healing and treating ocular surface diseases. Recent trials are investigating its safety and efficacy, particularly for diabetic patients with dry eye disease.

Intrathecal insulin delivery targets the central nervous system directly through spinal infusion.

Animal studies have shown improvement in diabetic neuropathy and neuronal signalling, but human trials remain limited.

CONCLUSION

Insulin delivery has progressed dramatically, evolving from painful injections to advanced closed-loop systems and non-invasive strategies such as inhaled, oral, buccal, nasal, transdermal, ocular, and intrathecal delivery. Advances in nanotechnology, microparticles, and drug formulations are promising to overcome current limitations like bioavailability and patient convenience, making future diabetes management more effective and patient-friendly. Continued innovation and clinical trials are essential to establish these newer routes as safe and reliable alternatives.

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Section 09

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Management of Complications in Diabetes

Chapter 28

Chronic kidney disease in people with diabetes - assessment, approach and newer evidence

Guliver Potsangbam

INTRODUCTION

The understanding and terminology for kidney disease in diabetes have significantly evolved. Historically, the term was Diabetic Nephropathy, defined clinically by albuminuria and retinopathy (especially in Type 1 diabetes), and linked to the classical pathology, diabetic glomerulopathy (glomerular basement membrane thickening, mesangial expansion, and podocyte loss). This original term was subdivided into "incipient nephropathy" (microalbuminuria, now moderately increased albuminuria or A2) and "overt nephropathy" (macroalbuminuria, now severely increased albuminuria or A3). These "incipient" and "overt" terms are no longer used due to a lack of specificity, though albuminuria severity remains a key risk indicator for cardiovascular disease and CKD progression.

The current preferred term is Diabetic Kidney Disease (DKD), used as a clinical diagnosis based on the presence of albuminuria, decreased estimated glomerular filtration rate (eGFR), or both. This change reflects the recognition of diverse histologic forms beyond classical glomerulopathy, including vascular and tubulointerstitial disease. Some guidelines, like KDIGO, use the term "Diabetes and CKD" when a biopsy is unavailable, emphasizing that other causes of CKD are common, particularly in type 2 diabetes mellitus (T2DM). While clinical data can suggest DKD, only a kidney biopsy can provide definitive confirmation.

The progression of diabetic kidney disease (DKD) is now recognized as highly variable, challenging the older view of a single, predictable pathway. Early in DKD, glomerular hyperfiltration—an abnormally high glomerular filtration rate (GFR)—is common and linked to increased risks of albuminuria and kidney function decline. Albuminuria, once considered the earliest and most important marker, can regress, and decreased estimated GFR (eGFR) may progress to advanced chronic kidney disease (CKD) even without increased albuminuria. Regression of albuminuria is more frequent in type 1 diabetes (59%) than in type 2 (22%), and is associated with a 22% reduction in the risk of end-stage kidney disease (ESKD) for a 30% reduction in albuminuria. The annual rate of eGFR decline in diabetes is faster than normal aging, and certain population groups experience higher rates of progression and ESKD. Overall, DKD progression is influenced by multiple factors, and both albuminuria and eGFR changes must be monitored for effective management.

Non-albuminuric Diabetic Kidney Disease (NADKD) is considered by reduced eGFR (<60 ml/ min/ 1.73 m^2) in diabetic patients without significant albuminuria (< 30 mg/ gm creatinine). It's present in 7–24% of patients with type 1 diabetes and 39–52% with type 2 diabetes and reduced eGFR. Prevalence is higher in women and increases with age. Associated factors include hypertension, dyslipidemia, smoking, and RAS inhibition. NADKD has a lower

prevalence of diabetic retinopathy (10-43% vs. 22-62% in albuminuric CKD) and a slower progression of kidney disease, with ESKD being rare without albuminuria. Renal biopsies show varied pathology, including classic diabetic glomerulopathy or predominant vascular/tubulointerstitial disease.

ASSESSMENT

The clinical evaluation of diabetic kidney disease (DKD) focuses on two main tests: albuminuria (urine albumin excretion) and estimated glomerular filtration rate (eGFR). Because DKD is often asymptomatic, routine annual testing is recommended using eGFR (via creatinine or cystatin C) and the urine albumin-to-creatinine ratio (UACR), following guidelines from the American Diabetes Association (ADA) and KDIGO. For type 1 diabetes, testing starts five years after diagnosis; for type 2, it begins at diagnosis. Abnormal results should be confirmed by repeat testing within three months. UACR is preferred over other urine tests for accuracy. Despite clear guidelines, surveillance rates—especially for UACR—are often low, which can impact risk-based management and treatment. Typically, urine sediment in DKD is bland, but findings like microscopic hematuria, dysmorphic red blood cells, or red blood cell casts may indicate nondiabetic kidney disease and require further investigation.

CLINICAL DIAGNOSIS OF DIABETIC KIDNEY DISEASE (DKD)

DKD is diagnosed clinically when persistent kidney function abnormalities occur in the context of long-standing diabetes, and there are no features suggesting another cause. The diagnosis relies on several key criteria such as Persistent Albuminuria and/or decreased GFR. These abnormalities must persist for at least three months to rule out transient issues. Notably, albuminuria is not required for DKD diagnosis, as some diabetic patients with decreased eGFR may have minimal albuminuria but still show histopathologic findings consistent with DKD. Long Duration of Diabetes or Established Diabetic Retinopathy: The presence of proliferative diabetic retinopathy in a patient with kidney disease is highly predictive of DKD, even with a short duration of diabetes.

A kidney biopsy should be considered if any of the following are present as these may be indicative of alternate aetiologies:

- Severely increased (A3) albuminuria within five years of T1D onset or before T2D onset.
- Red blood cell casts, dysmorphic red blood cells, or white blood cell casts in urine sediment.
- Presence of another systemic disease commonly associated with kidney disease (e.g., systemic lupus erythematosus).
- Sudden increase in albuminuria or rapid decline in eGFR.
- Nephrotic-range proteinuria (albuminuria >3.5 g/day) is atypical in diabetes of less than 10 to 15 years' duration.

Studies show a significant rate of non-DKD diagnoses even when biopsies are restricted to patients with suspected alternate diagnoses. In one cohort, one-third showed classic diabetic glomerulopathy alone, one-third showed diabetic glomerulopathy plus non-DKD, and one-third showed non-DKD alone. Common non-DKD findings include acute tubular necrosis, immune-mediated glomerular diseases, hypertensive nephrosclerosis, and focal segmental glomerulosclerosis.

NEWER EVIDENCE: THE THERAPEUTIC REVOLUTION

Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT) convincingly demonstrated a reduction in the need for

hospitalization for heart failure (HHF) in people with CKD and T2D with the use of these drugs. Thus, to protect from kidney disease progression in people with T2DM and albuminuria, angiotensin receptor blockers (ARBS) became the standard of care. The most significant recent advancements involve the introduction of new drug classes that provide cardiorenal protection independent of and in addition to their glucose-lowering effects.

SGLT2 Inhibitors: The Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors (e.g., dapagliflozin, empagliflozin) represent a paradigm shift and are now recommended as first-line therapy for people with T2DM and CKD or those at high cardiovascular risk. These drugs block the reabsorption of sodium and glucose in the proximal renal tubule. This increases sodium delivery to the macula densa, which in turn activates the tubulo-glomerular feedback mechanism, causing afferent arteriolar vasoconstriction. This hemodynamic effect lowers intraglomerular pressure, effectively mitigating the hyperfiltration and stress that drives DKD progression. Clinical Evidence: Landmark trials (e.g., DAPA-CKD, EMPA-KIDNEY) have definitively shown significant reductions in the composite renal outcome (e.g., ESKD, decline in eGFR) and the risk of cardiovascular death and hospitalization for heart failure (HF), even in patients without diabetes. An expected, small, transient drop in eGFR upon initiation is a sign of therapeutic effectiveness (lowering hyperfiltration), not kidney injury.

Non-Steroidal Mineralocorticoid Receptor Antagonists (ns-MRA): This is class of agents, with Finerenone being the first approved, targets kidney damage through a distinct anti-inflammatory pathway. It selectively blocks the mineralocorticoid receptor (MR), which counteracts the harmful effects of hyperaldosteronism, specifically reducing inflammation and fibrosis in the kidney and heart. A key advantage over older, steroidal MRAs (spironolactone) is a lower risk of severe hyperkalemia. It is recommended for patients with T2DM and CKD (with albuminuria) who are already on maximum-labelled or tolerated RAAS blockade (ACEi or ARB), to further reduce CKD progression and cardiovascular risk. Careful monitoring of serum potassium is essential.

GLP-1 Receptor Agonists: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (e.g., semaglutide, dulaglutide) are anti-diabetic agents with significant benefits beyond glycemic control. Renoprotective Effects: While they enhance insulin secretion and promote satiety, their renoprotective effects are mediated primarily by significant cardiovascular risk reduction (reducing atherosclerotic events), reduction of systemic inflammation, and a direct reduction in albuminuria. These agents are recommended for people with T2DM and CKD to reduce Major Adverse Cardiovascular Events (MACE) and CKD progression. They are often used as a second-line agent or added to SGLT2 inhibitors and RAAS blockade, especially in patients requiring substantial weight loss or who have established atherosclerotic CVD.

The new standard of care for most eligible patients is a quadruple therapy approach, often called the "Four Pillars" of Cardiorenal Protection: RAAS blockade, SGLT2 Inhibitors, ns-MRA(Finerenone) and GLP-1R agonists. More recently, the CONFIDENCE trial has elegantly shown that among persons with both chronic kidney disease and type 2 diabetes, initial therapy with finerenone plus empagliflozin led to a greater reduction in UACR than either treatment alone. So, simultaneous initiation of both drugs should be strongly considered in all eligible patients.

CONCLUSION

Education, adherence and access are the key barriers to implementation of research into practice. Despite decades-old guidelines, screening of kidney disease is suboptimal. Thus a large fraction of patients with CKD who have T2D are left undiagnosed. It needs to be emphasised that UACR(Urinary albumin

creatinine ratio) measurement is similar to the measurement of BP or LDL cholesterol, because it should trigger treatments that reduce cardiovascular and kidney risks in people with T2D, is important. Without screening, effective treatments cannot be prescribed. Access to therapies has become an important barrier to implementing therapies. Adherence to treatments is much more complicated, especially for chronic diseases, and the importance of taking these treatments on a long-term basis cannot be overemphasized. Lifestyle modifications are the foundation on which the pillars are built; the foundation is for all people with T2D and CKD. Lifestyle modifications cost little, but adherence to these lifestyle changes is difficult. On the other hand, building the pillars of therapy is easy, but is associated with increasing costs as we move from the first to the fourth pillar.

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Chapter 29

Approach to Foot Care and Diabetic Foot Risk Stratification System

Ritesh Agarwal

INTRODUCTION

Diabetes mellitus is one of the most significant chronic diseases globally, with an estimated prevalence exceeding 500 million individuals by 2030. Diabetic related complications contribute substantially to morbidity, mortality and healthcare costs. Among the most debilitating and costly complications is diabetic foot disease, which encompasses a spectrum from callus formation and neuropathic ulceration to severe infection, gangrene and amputation. It is estimated that between 15–25% of patients with diabetes will develop a foot ulcer during their lifetime and diabetic foot complications account for up to 50–70% of all non-traumatic lower limb amputations worldwide.

The diabetic foot problem is not merely a localized disorder but reflects systemic pathophysiology, including neuropathy, peripheral arterial disease (PAD), impaired wound healing, and infection susceptibility. Its consequences extend beyond physical disability, as amputation is associated with reduced quality of life, loss of productivity, psychological distress, and increased mortality. Indeed, five-year mortality after a major lower limb amputation approaches 70%, a figure comparable to advanced cancer. Recognizing these profound impacts, international guidelines, notably those of the International Working Group on the Diabetic Foot (IWGDF), American Diabetes Association (ADA), and International Diabetes Federation (IDF), emphasize structured risk assessment, stratification, and preventive foot care as cornerstones of management. Early identification of "at-risk" feet, targeted education, appropriate footwear, timely vascular evaluation, and multidisciplinary team care have been shown to markedly reduce ulceration and amputation rates.

EPIDEMIOLOGY OF DIABETIC FOOT COMPLICATIONS

The global burden of diabetic foot disease is immense. Each year, approximately 2% of individuals with diabetes develop a new foot ulcer, and recurrence rates are extremely high: 40% within one year after healing, 65% within three years, and 75% within five years. The prevalence of active ulceration at any given time is estimated at 4–10%. There are marked regional differences. In high-income countries, widespread access to multidisciplinary care and podiatry services has lowered amputation rates over recent decades. In contrast, low- and middle-income countries (LMICs) often face late presentations, limited access to vascular surgery or podiatry, and poor availability of therapeutic footwear. In South Asia, ulcer prevalence is higher, and up to 80% of amputations occur following a diabetic foot infection.

Preventive foot care and risk stratification, though resource-intensive at the outset, are consistently cost-effective interventions when compared with the high direct and indirect costs of ulcer treatment and limb loss.

PATHOPHYSIOLOGY UNDERLYING DIABETIC FOOT RISK

Neuropathy

Peripheral neuropathy is the most important risk

factor for foot ulceration. It results from metabolic and microvascular changes induced by chronic hyperglycemia, leading to axonal degeneration and demyelination. The main components include:

1. Sensory neuropathy: Loss of protective sensation (LOPS) renders the patient unable to perceive pain, temperature, or pressure. Minor trauma, such as ill-fitting shoes, may go unnoticed until a significant wound develops.

Motor neuropathy – Imbalance between flexor and extensor muscles of the foot leads to deformities such as hammertoes, claw toes, and prominent metatarsal heads. These increase focal plantar pressure, creating sites prone to ulceration.

Autonomic neuropathy – Denervation of sweat glands causes dry, fissured skin, reducing natural barrier protection. Arteriovenous shunting may impair capillary perfusion.

The cumulative effect is the "neuropathic foot," characterized by deformity, insensate skin, callus formation, and vulnerability to injury.

Peripheral Arterial Disease (PAD)

PAD is another critical determinant of ulceration and poor healing. Diabetes accelerates atherosclerosis, affecting distal arteries below the knee and compromising blood supply to the foot. The combination of neuropathy and PAD is especially dangerous: trauma is unnoticed, and healing capacity is reduced. PAD prevalence among people with diabetes is estimated at 20–30%, with higher rates in older populations.

Infection Susceptibility

Impaired neutrophil function, vascular insufficiency, and poor tissue oxygenation predispose to infection. Once an ulcer is established, bacterial colonization can progress rapidly to cellulitis, deep tissue infection, or osteomyelitis. Diabetic foot infections are the most common precipitant of non-traumatic amputations.

Evolution of Guidelines and Risk Stratification Systems

Recognition of the preventable nature of many diabetic foot complications has led to decades of effort in guideline development. Early efforts (1980s–1990s) emphasized regular foot inspection and patient education but lacked structured stratification.

IWGDF (founded 1999) introduced standardized international guidelines, updated every four years. The 2023 IWGDF prevention guideline formalized a risk classification system from 0–3 and surveillance intervals. ADA published recommendations for comprehensive foot examination and risk assessment in 2008, subsequently revised into the Modified ADA risk classification (Very Low, Low, Moderate, High, Urgent). IDF guidelines echo these frameworks, adapted for diverse health system capacities worldwide.

Today, risk stratification is central: it enables targeted surveillance, rational allocation of resources, and tailoring of interventions to patient needs.

Clinical Approach to Diabetic Foot Care

IWGDF Risk Stratification

Risk Category	Criteria	Recommended Follow-up
0 (Low)	No neuropathy or PAD	Annual foot exam
1 (Moderate)	Neuropathy ± deformity	Every 3-6 months
2 (High)	Neuropathy + PAD or deformity	Every 1-3 months
3 (Very High)	Previous ulcer or amputation	Every 1-3 months, specialist referral

Initial Screening

All patients with diabetes should undergo foot screening at diagnosis and at least annually thereafter. Screening should cover history, inspection, neurological testing, and vascular assessment.

History: Prior ulcer or amputation, duration of diabetes, smoking, symptoms of neuropathy or claudication.

Inspection: Skin integrity, callus, deformities, footwear.

Neuropathy assessment: 10-g monofilament, vibration perception, pinprick, temperature.

Vascular assessment: Palpation of dorsalis pedis and posterior tibial pulses, ABI measurement if available.

Risk Stratification

Based on findings, patients are assigned a risk category. The IWGDF 0–3 model is widely used:

- Risk 0: No LOPS, no PAD.
- Risk 1: LOPS or PAD.
- Risk 2: LOPS with PAD, or deformity, or pre-ulcerative lesion.
- Risk 3: History of ulcer or amputation, or multiple risk factors.

The ADA model adds an "Urgent" category for active pathology requiring immediate care (12).

Surveillance Intervals

- Risk 0: annually
- Risk 1: every 6–12 months
- Risk 2: every 3–6 months
- Risk 3: every 1–3 months

Risk Categories in Detail

Risk 0: Very Low Risk

These individuals have intact protective sensation and no PAD. The main goals are education and annual re-assessment. Footwear should be checked, barefoot walking discouraged, and hygiene reinforced.

Risk 1: Low Risk

Presence of either LOPS or PAD warrants more vigilance. Patients should be examined every 6–12 months. Education is intensified, and footwear selection becomes more critical.

Risk 2: Moderate Risk

This category includes those with neuropathy plus deformity, PAD, or pre-ulcerative lesions. Interventions include therapeutic footwear, orthoses, callus debridement, and possibly skin temperature monitoring. Reviews every 3–6 months are required.

Risk 3: High Risk

Those with prior ulceration or amputation are at greatest risk of recurrence. They require multidisciplinary follow-up every 1–3 months, therapeutic footwear, and often custom orthoses. Daily temperature monitoring and early intervention for any lesion are emphasized.

Urgent Category

Active ulcer, infection, or acute Charcot foot constitutes a medical emergency. Prompt referral to specialist foot services, vascular assessment, and initiation of infection management are mandatory.

Preventive and Therapeutic Interventions

Patient Education

Education must be individualized, practical, and culturally appropriate. Core messages include daily self-inspection, washing and drying feet, moisturizing to prevent fissures, proper nail care, avoiding barefoot walking, and recognizing warning signs. Repetition and reinforcement are essential for behavioral change.

Footwear and Offloading

Proper footwear is fundamental. For risk 0–1, well-fitting shoes with cushioning are sufficient. For higher risk, therapeutic shoes with proven plantar pressure relief are recommended. Total contact casting remains the gold standard for offloading

active plantar neuropathic ulcers, while removable cast walkers, orthoses, or felt padding are alternatives.

Callus and Nail Care

Regular debridement of callus by trained personnel reduces plantar pressure and ulcer risk. Nail care, especially in thickened or fungal nails, prevents trauma and infection.

Vascular Optimization

For patients with PAD, aggressive cardiovascular risk factor modification is vital: smoking cessation, lipid lowering, antiplatelet therapy, and tight glycemic control. Where indicated, revascularization through angioplasty or bypass can be limb-saving.

Infection Management

Infection must be recognized early and treated aggressively. Mild infections may be managed with oral antibiotics, while moderate to severe infections require hospitalization, intravenous therapy, and often surgical debridement. Osteomyelitis may necessitate prolonged antibiotics or bone resection.

Multidisciplinary Foot Care

Optimal outcomes are achieved in dedicated multidisciplinary foot clinics, where endocrinologists, podiatrists, vascular surgeons, orthopedists, infectious disease specialists, and wound care nurses collaborate. Such teams significantly reduce amputation rates.

Broader Perspectives

Health Systems and Public Health

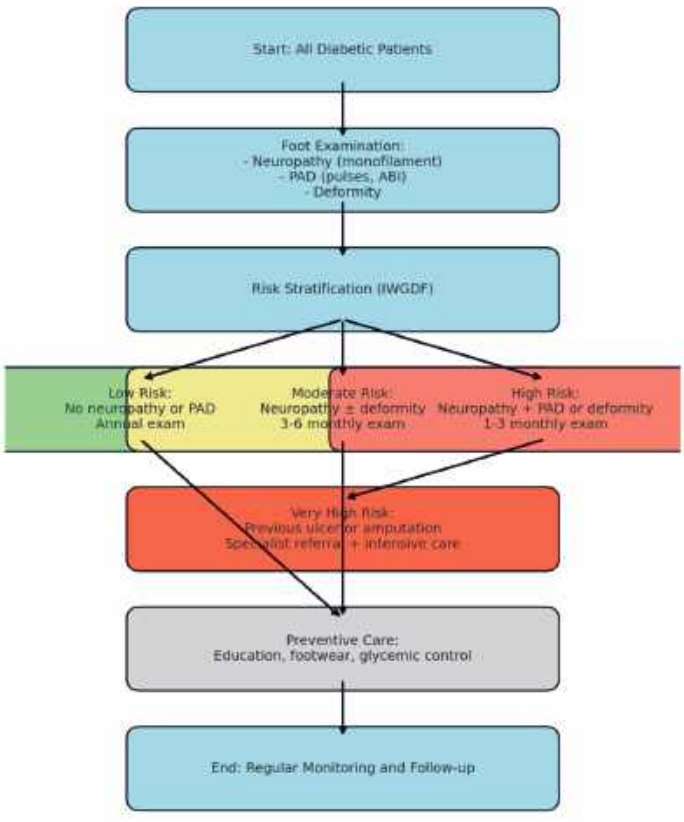
Implementing widespread foot screening and preventive care requires system-level planning. Training of primary care workers, use of standardized screening tools, integration into diabetes clinics, and referral pathways to specialized centers are necessary. Public health strategies include awareness campaigns, subsidization of therapeutic footwear, and national registries for diabetic foot outcomes. Cost-effectiveness analyses consistently show that preventive programs are cheaper than managing advanced ulcers or amputations.

Technological Innovations

Recent years have seen promising technologies:

- Smart insoles that detect high plantar pressures and alert the user.
- Infrared thermography for early detection of hot spots indicating inflammation.
- Telemedicine platforms allowing remote foot monitoring.
- Artificial intelligence (AI) algorithms predicting ulcer risk based on electronic health records and foot images.

While evidence is emerging, integration into routine care could revolutionize diabetic foot prevention. **[Flow chart 1: Diabetic Foot Screening and Risk Stratification]**



CHALLENGES AND FUTURE DIRECTIONS

Despite advances, multiple challenges remain. In many regions, podiatry services are scarce, footwear is unaffordable, and patients present late. Adherence to daily self-care is often suboptimal. Cultural practices such as barefoot walking persist. Moreover, healthcare providers may lack training in foot screening. Future directions include scaling up training programs, low-cost offloading solutions, mobile health interventions, and stronger health system integration. Research priorities involve evaluating cost-effectiveness in LMICs, validating AI-based risk tools, and testing culturally adapted educational strategies.

CONCLUSION

Diabetic foot disease remains a major source of preventable morbidity and mortality. A systematic approach, beginning with comprehensive foot screening, followed by structured risk stratification and tailored surveillance is central to prevention. Education, footwear, callus care, vascular optimization, and multidisciplinary involvement reduce ulceration and amputation. However, success depends on implementation across diverse healthcare settings, supported by education, resources, and innovation. By embedding risk stratification systems into routine diabetes care, the devastating consequences of diabetic foot complications can be substantially reduced.

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Chapter 30

Validated Approach and Implementation Methodology of Diabetes-Related Eye Disease Before Referral to an Ophthalmologist

Ayondyuti Bora

INTRODUCTION

India remains at the forefront of the global diabetes epidemic, with recent estimates suggesting upwards of 100 million people living with diabetes in the coming decade. According to the latest position statements, the prevalence of diabetic retinopathy (DR) among known persons with diabetes is around 12.5 % (with approximately 4 % having vision-threatening DR) in India. Risk factors for DR progression include longer diabetes duration, age >40 years, high systolic BP, poor glycaemic control (high HbA1c), anemia, hyper-cholesterolemia, obesity, low-fiber diet, albuminuria, neuropathy, and foot ulceration. Unlike other causes of visual impairment such as cataract, refractive error or corneal blindness, DR often remains asymptomatic until relatively advanced. Thus, by the time visual symptoms develop, irreversible retinal damage may have already occurred and treatments—such as laser photocoagulation or intravitreal anti-VEGF (vascular endothelial growth factor) therapy—become imperative. Given this silent progression, a structured, validated screening and referral methodology is essential in India, where specialty ophthalmic resources are unevenly distributed and the burden of undiagnosed diabetes remains high.

RATIONALE FOR PRE-REFERRAL SCREENING OF DIABETES-RELATED EYE DISEASE

The goal of screening in DR is to identify individuals with sight-threatening diabetic retinopathy (STDR) (which includes severe non-proliferative DR, proliferative DR or clinically significant macular oedema) at a stage when timely treatment can prevent visual loss. A screening framework is justified because:

- DR has a latent (asymptomatic) stage and progresses gradually.
- Treatment options exist that improve outcomes if applied early.
- The vast number of people with diabetes in India and the relative shortage of retina specialists mean that opportunistic or ad-hoc referral alone will miss many.
- Country-specific evidence shows under-screening: a large number of people with diabetes have never had an eye exam.

Hence, a validated pre-referral screening strategy, aligned with India's healthcare system and resource constraints, is essential.

DR SCREENING AS A PART OF DIABETES CARE

– Incorporation of DR screening as a standard of care for diabetes with regular referral to an ophthalmologist for DR screening.

– The second option is that instead of sending every patient to the Ophthalmologist for DR screening, an in-clinic screening can be done using a fundus camera with Artificial Intelligence (AI) or without AI using teleophthalmology.

– If the patient has a referral DR, then is sent for further evaluation and management to the in-house ophthalmologist.

DR SCREENING INTERVALS IN PEOPLE WITH DIABETES

Indian data on DR incidence remain limited. The SN-DREAMS II study reported a 4-year incidence of 9.2% for DR, 2.6% for DME, and 5.0% for STDR. Among those with baseline DR, incidence rose to 11.5% for DME and 22.7% for STDR, emphasizing that pre-existing DR is a strong predictor of progression. Physicians should ensure that all patients with diabetes undergo a comprehensive eye examination at least once a year, regardless of glycaemic control or disease duration. Screening frequency depends on the type of diabetes and DR severity, as per the International Clinical DR and DME Severity Scale. Intervals may be individualized based on systemic factors such as glycaemic control, blood pressure, lipids, and comorbidities.

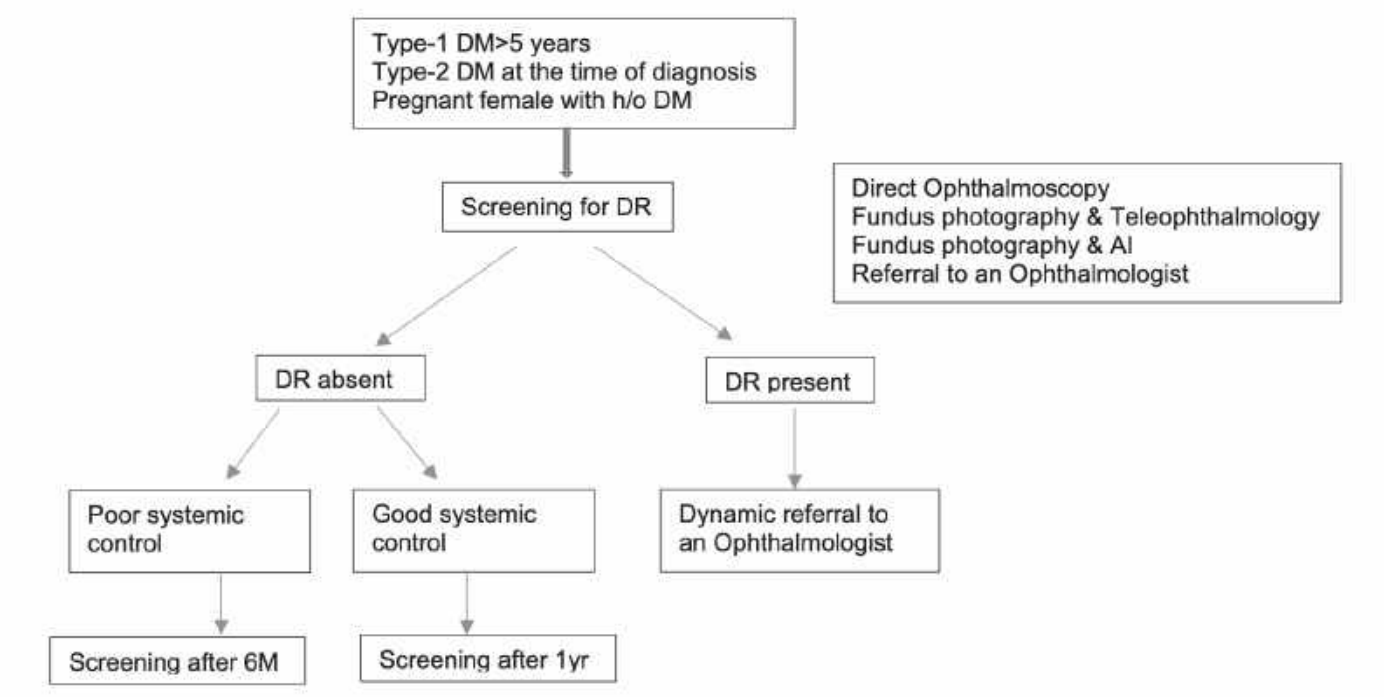
All individuals with diabetes are at risk of DR.

- **Type 2 diabetes:** screen at diagnosis.
- **Type 1 diabetes:** start screening after age 11 and 2–5 years of disease.
- **Pregnant women with diabetes:** screen before conception and in the first trimester.

SCREENING MODELS

The gold standard for assessing diabetic retinopathy (DR) severity is stereoscopic seven-field fundus photography through dilated pupils, as established by the Early Treatment Diabetic Retinopathy Study (ETDRS). However, in India—where ophthalmology services are insufficient for the large diabetic population—a stepwise, scalable screening approach is necessary.

The strategy begins with mass, population-based screening to raise awareness among patients, the public, and healthcare workers. Those identified with DR should then be referred to special prioritizers for monitoring and treatment. Although few programs meet ETDRS standards, India must prioritize the identification of STDR using feasible, cost-effective alternatives. Telemedicine and non-mydriatic fundus cameras have revolutionized DR screening,



Flow chart for DR screening at a Physician clinic

especially in resource-limited settings. Yet, small pupils and cataracts can compromise image quality; thus, mydriatic screening should be encouraged wherever possible, unless wide-angle non-mydriatic cameras are available.

The American Telemedicine Association (ATA) outlines four key components for DR telehealth programs:

1. Image acquisition
2. Image review and evaluation
3. Patient care supervision
4. Image and data storage

These elements ensure consistent quality, reliability, and patient safety.

SCREENING MODELS FOR DIABETIC CLINICS WHERE THERE IS NO FACILITY FOR SCREENING TO BE DONE BY AN OPHTHALMOLOGIST

In practice, DR screening in India can be implemented through two main pathways:

- Community-based models, which emphasize outreach and early detection.
- Hospital-based models, which focus on structured follow-up, management, and integration with diabetes care services.

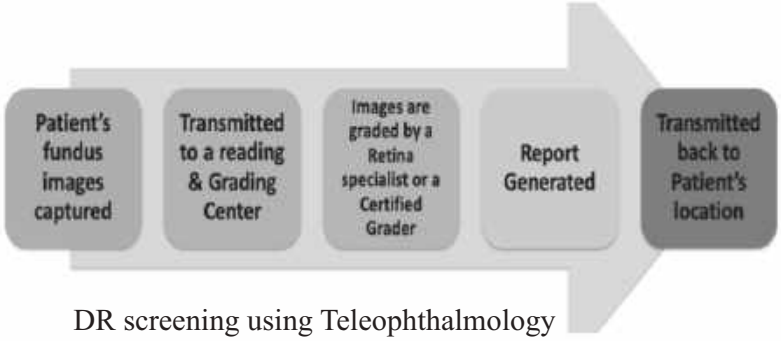
DR screening in physician clinics is now simple and affordable using fundus photography or AI-based image analysis with a camera, trained technician, and internet access. Skills can be upgraded through certified DR courses such as those offered by (Indian Health Outcomes, Policy, and Economic Research) IHOPE. In clinics without on-site ophthalmologists, DR screening can be done by:

- Direct ophthalmoscopy**:** Physicians trained during undergraduate studies can perform basic retinal exams.
- Tele-screening**:** Retinal images captured using portable or non-mydriatic fundus cameras by trained staff or optometrists can be sent to remote ophthalmologists or graders for DR assessment, with reports typically returned within hours to days.

AI-BASED TELE-SCREENING FOR DR

Artificial intelligence has revolutionized DR screening by accurately grading retinal images comparable to a retina specialist. AI systems can instantly classify cases as referable or non-referable DR and generate reports within minutes, enabling physicians to counsel patients immediately. Commercial AI software shows high sensitivity and specificity, though reports include a disclaimer that results are for screening only and not for medicolegal use. The primary goal is early detection and timely referral to an ophthalmologist, improving screening compliance and reducing vision loss. Clinics linked with referral centers can ensure prompt management of detected cases.

QUALITY ASSURANCE STANDARDS FOR DR SCREENING



DR screening using Teleophthalmology

Quality assurance is essential to ensure reliability and effectiveness of any DR screening program. Key standards include:

- Informed consent must be obtained before image capture.
- Use a high-quality, easy-to-operate fundus camera with a wide field of view (130–200°).
- Capture two retinal images per eye (macula-

and disc-centred), plus an optional anterior segment image for assessing media clarity.

- While non-mydriatic cameras are preferred, mydriasis improves image gradeability and reduces ungradable images.
- Grading should be done by certified human graders; if AI is used, it must be validated and approved, with a screening-only disclaimer.
- AI grading should assist but not replace physician judgment.
- Screening reports should be promptly available to facilitate timely referral.
- Maintain secure backup and storage of images and diagnostic data, ideally with an alert system for missed follow-ups.
- Implement a recall system (calls/SMS reminders) to ensure annual rescreening and continuity of care.

CREATING PUBLIC AWARENESS FOR DR

Raising public awareness is vital to prevent blindness from diabetic retinopathy (DR). Physicians should consistently emphasize the importance of regular DR screening during diabetes consultations and insist on screening reports as part of routine follow-up. Educational posters in clinic waiting areas and informative pamphlets with visual aids can effectively engage patients and caregivers. DR screening must be integrated into the standard of diabetes care, ensuring that every patient understands the risk of vision loss and the benefits of early detection.

ROLE OF METABOLIC CONTROL IN THE MANAGEMENT OF DR

Good metabolic control including blood sugar level, blood pressure and dyslipidaemia retards the progression of DR. Higher initial levels of HbA1c increase the risk of DR. Intensive glycaemic control (HbA1c < 7%), especially in the early stages of onset of diabetes, has a profound impact on the progression of DR and reduces the risk of developing DR by 27%. Control of high lipids reduced the risk of developing hard exudates and decrease the associated vision loss. In type 2 DM, there is a decrease in DR by 31% for every 1% decrease in HbA1c and a decrease in vitreous haemorrhage by 11% for every 10 mmHg decrease in systolic blood pressure. It is recommended that diabetics with hypertension regularly monitor their blood pressure and keep it below 140/80 mm Hg.

CONCLUSION

India bears a growing burden of diabetes and, consequently, a rising incidence of diabetic retinopathy (DR), a major cause of preventable blindness. The asymptomatic nature of early DR and low public awareness often delay diagnosis until vision-threatening stages develop. By uniting efforts across disciplines and healthcare levels, India can move toward a future where preventable blindness from DR is virtually eliminated, ensuring that every person with diabetes has access to early diagnosis and sight-saving interventions.

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Chapter 31

Cardiovascular Disease and Risk Management in Diabetes – Focus on Diabetic Cardiomyopathy – Early Biomarkers and Therapeutic Intervention

Alokjyoti Malakar

INTRODUCTION

As the number of Diabetes Mellitus is increasing day by day, it is an alarming risk factor for development of cardiovascular disease (CVD) such Atherosclerotic cardiovascular Disease (ASCVD), heart failure (HF), atrial fibrillation (AF), stroke, aortic and peripheral artery diseases. In addition, diabetes is a major risk factor for chronic kidney disease (CKD), which is associated with increase in CVD. Numerous studies have shown the efficacy of managing individual cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Under the current era of comprehensive risk factor management, cardiovascular morbidity and mortality have notably decreased in people with b type 2 diabetes. Although great advances in treatment and prevention have promoted significant reductions in diabetes-related coronary artery disease mortality in developed countries, cardiovascular morbidity and mortality still remain high in the majority of patients with diabetes in most of the developing countries.

Newer researches prove that there is a common pathophysiology and interrelationship of cardiometabolic risk factors leading to both adverse cardiovascular and adverse kidney outcomes in people with diabetes, including ASCVD, heart failure, and chronic kidney disease (CKD).

Reasons to concurrently consider cardiovascular and kidney comorbidities in the management of people with diabetes include not only the common metabolic risk but also the major benefit observed across the spectrum of cardiovascular disease, heart failure, and renal outcomes in people with type 2 diabetes treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Therefore, in addition to the management of hyperglycemia, hypertension, and hyperlipidemia, treatment with Sodium glucose transporter-2 (SGLT2) inhibitors and/or Glucagon like peptide 1 receptor agonists (GLP-1 RA) that have demonstrated significant benefit in risk reduction and improved cardiovascular and kidney outcomes in people with type 2 diabetes (Fig. 1).

Glucose control in individuals with diabetes at high CV risk is a complex area and current evidence indicates the need to address multiple glycaemic measures including insulin and conventional oral anti diabetic medication with cardiac safety and newer drugs like SGLT2 inhibitors and GLP-1 RAs, personalizing HbA1c targets, minimizing hypoglycaemic exposure, and limiting glucose variability.

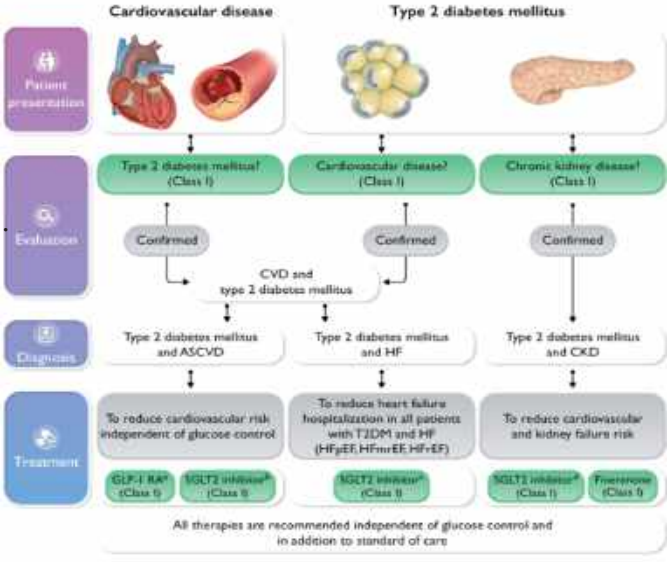

Fig. 1. Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations. Adapted from ESC 2023

HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for ASCVD, heart failure, and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications.

LIPID MANAGEMENT

People with type 2 diabetes have an increase prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes.

LIFESTYLE INTERVENTION

Lifestyle intervention, including weight loss in people with overweight or obesity, increased physical activity and exercise, and medical nutrition therapy, allows some individuals to reduce ASCVD risk factors. Nutritional intervention should focus on application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern. Glycemic control may also beneficially modify plasma lipid levels, particularly in people with very high triglycerides and poor glycemic control.

Smoking cessation is a very important lifestyle intervention in patients with T2DM with or without CVD with evidence suggesting a 36% reduction in mortality in CVD patients.

DIABETIC CARDIOMYOPATHY (DCM)

DCM has been defined as myocardial dysfunction without concomitant coronary atherosclerosis, valvular heart disease and elevated blood pressure. Defining Diabetic Cardiomyopathy correctly is quite challenging, as most patients with type 2 diabetes mellitus (T2DM) have cardiovascular disease. The incidence of diabetic cardiomyopathy increases in proportion to the onset of diabetes in the population.

PATHOPHYSIOLOGY

The exact pathophysiological mechanisms are not very well known till now because of the complexity. The pathophysiology involves multiple mechanisms, including metabolic derangements, oxidative stress, inflammation, and fibrosis. Impaired insulin signalling plays a crucial role in the development of DCM. Insulin resistance, a hallmark of type 2 diabetes, leads to inadequate glucose uptake by cardiomyocytes, resulting in energy deprivation and metabolic disturbances (Figure 2).

Specific biomarkers that can aid in diagnosis are still being investigated. In recent years, cardiac microRNAs (miRNAs) have emerged as crucial regulators in the development of DCM. These miRNAs target specific mRNAs that are altered in DCM, playing significant roles in regulating genes associated with the key pathophysiological pathways of DCM, such as hypertrophy, apoptosis, and fibrosis. There are some inflammatory and metabolic biomarkers those are linked to cardiac alteration in individual with DM, such as mitral annular calcification (MAC) that can be picked up early by echocardiography in diabetic patients.

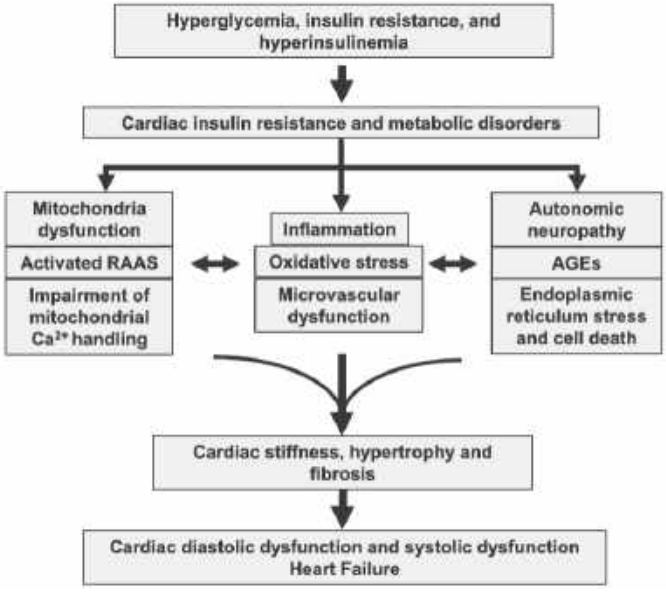

Figure 2. Pathophysiological mechanisms of diabetic cardiomyopathy. (Adapted from-Guanghong Jia, Michael A. Hill, James R. Sowers: Diabetic Cardiomyopathy. An Update of Mechanisms Contributing to This Clinical Entity, Circ Res. 2018;122:624-638. DOI: 10.1161/CIRCRESAHA.117.311586.)

Alterations in cardiac metabolism, such as increased fatty acid utilization and reduced glucose oxidation, contribute to the development of myocardial lipotoxicity. Excessive accumulation of lipids within the cardiomyocytes leads to mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and impaired contractile function ultimately resulting in diabetic cardiac dysfunction. Chronic persistent hyperglycemia also has a central role in the pathogenesis of DCM. Elevated glucose levels contribute to the formation of advanced glycation end-products (AGEs), which promote oxidative stress and inflammation. AGEs interact with their receptors (RAGE) on car diomyocytes and cardiac fibroblasts, triggering intracellular signaling pathways that promote fibrosis, hypertrophy, and apoptosis. Inflammation and immune dysregulation are important contributors to the development and progression of DCM. The release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF) and interleukin-6 (IL-6), is increased in diabetic patients. These cytokines activate intracellular pathways involved in fibrosis, hypertrophy, and myocardial dysfunction. Increased production of profibrotic factors, such as transforming growth factor- beta (TGF-), promotes the activation of cardiac fibroblasts and subsequent collagen synthesis. Cardiac fibrosis disrupts normal myocardial architecture, leading to impaired diastolic and systolic function.

Table 1 Diagnostic Method of DCM

Method	Evaluation	Evaluated Criterion
Echocardiography	Functional	Mitral inflow for diastolic function
		Tissue Doppler imaging for diastolic and systolic function
	Structural	In two-dimensional echocardiography LV hypertrophy
Cardiac PET	Metabolic and hemodynamic	Myocardial metabolic abnormality and disordered blood flow
Cardiac MRI	Functional	Late gadolium-enhancement for diastolic and systolic function
	Structural	Myocardial steatosis, LV hypertrophy
	Metabolic	Magnetic resonance spectroscopy for myocardial TG content and PCr/ATP
Coronary angiography	Functional and hemodynamic	Mean PCWP and LVEDP for diastolic function, microvascular coronary artery disease
Serology	Functional	mi-RNA for contractile function
		BNP for diastolic and systolic function
		Troponin for LV dysfunction
	Structural	MMPs and TIMPs for myocardial fibrosis
MAC biomarkers	Inflammatory and metabolic	Increase in TNF-alpha and HOMA-C peptide levels

DIAGNOSIS

The early diagnosis of DCM is essential for controlling the development of heart failure, but there are challanges due to the lack of precise diagnostic standards. The diagnosis of DCM has been enhanced by advances in imaging technologies, including cardiac MRI, echocardiography, and the use of biomarkers (Table 1); however, the histological investigation may still be necessary for a conclusive diagnosis.

In the early subclinical period significant histological and functional changes may occur. So, it is beneficial to make early diagnosis during the asymptomatic period. Structural alterations can be detected using both invasive and non-invasive methods, while functional changes are typically identified through

echocardiography. Metabolic changes in the diabetic heart can be characterized by tools like magnetic resonance spectroscopy, positron emission tomography (PET) and single-photon emission computed tomography.

Specific biomarkers that can aid in diagnosis are still being investigated. In recent years, cardiac microRNAs (miRNAs) have emerged as crucial regulators in the development of DCM. These miRNAs target specific mRNAs that are altered in DCM, playing significant roles in regulating genes associated with the key pathophysiological pathways of DCM, such as hypertrophy, apoptosis, and fibrosis. There are some inflammatory and metabolic biomarkers those are linked to cardiac alteration in individual with DM, such as mitral annular calcification (MAC) that can be picked up early by echocardiography in diabetic patients.

SGLT2 inhibitors demonstrated promising cardioprotective effects, reducing the rate of cardiovascular events in high-risk patients with DM and optimizing clinical outcomes in subjects affected by heart failure (HF) irrespective of LVEF and diabetic condition. SGLT2i contributes to improved heart function by glucose lowering effect, natriuretic effects, and attenuation of oxidative stress, inflammation, and fibrosis in the heart.

Glucagon-like peptide-1 (GLP-1) receptor agonists can enhance myocardial sensitivity to insulin, improve the glucose uptake rate, promote myocardial energy metabolism, and inhibit cardiomyocyte apoptosis, which contributes to the treatment of DCM. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as linagliptin can prevent cardiac dysfunction by inhibiting the Nlrp3/ASC inflammasome and modulating the JAK/STAT signaling pathway.

Along with these newer strategy in prevention and management of Diabetic Cardiomyopathy, the conventional treatment with ACE inhibitor, ARBs, Neprilysin inhibitors, betablockers, Aldosterone antagonist are the mainstay of therapy in patient with heart failure with DCM.

CONCLUSION

DCM is a specific form of cardiac dysfunction that occurs in diabetic individuals, independent of other known cardiac diseases. The pathophysiology of DCM involves multiple mechanisms, including metabolic impairment, oxidative stress, inflammation, and fibrosis. Early diagnosis and management of DCM are important. Diagnosis can be challenging due to the asymptomatic nature of DCM in its early stages, but advanced imaging techniques and biomarkers offer valuable tools for detection. Antidiabetic drugs like, SGLT2i, GLP1RA have shown beneficial effects on DCM by modulating various pathways involved in DCM physiopathology. Novel therapeutical strategies, like gene therapy and non-coding RNA, ameliorate cardiac metabolism and seem to be promising in hindering DCM-related cardiac dysfunction.

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Section 10

Section Editor : **Ksh. Achouba Singh & Avik Chakraborty**

Management of Diabetes in Hospital

Chapter 32

Approach to Glucose Lowering in Hospitalized patients with Diabetes

Bidita Khandelwal
Devraj Saha

INTRODUCTION

Hyperglycemia in hospitalised patients, with or without diabetes, is associated with increased morbidity and mortality and a substantial increase in the health care costs. Due to the complexity of the inpatient glycemic control factors, "one size fits all" approach is not always effective. Patient centred, evidence based, effective yet save and less complex strategies are required. Patient education, involvement and use of technology facilitate in achieving the goals.

DEFINITIONS

The American Diabetes Association (ADA) defines Hyperglycemia in hospitalized individuals as "blood glucose levels >140 mg/dL (>7.8 mmol/L)" Hb A1C value ≥6.5% (≥ 48 mmol/mol) on admission suggests preexisting diabetes. ADA, American Association of Clinical Endocrinologists (AACE) consensus on inpatient hyperglycemia and British Diabetes Societies for Inpatient Care, defines stress hyperglycemia or hospital-related hyperglycemia as "any blood glucose concentration >140 mg/dl (>7.8 mmol/l) in patients without a prior history of diabetes" Stress hyperglycemia is typically transient and resolves as the acute stress resolves, however some may develop confirmed diabetes at 6-12 months after discharge." Level 1 hypoglycemia is defined as a "glucose concentration of 54–69 mg/dL (3.0–3.8 mmol/L). Level 2 hypoglycemia is defined as a glucose concentration <54 mg/dL (<3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery."

PREVALENCE

People with diabetes have a 35% greater chance of referral for elective operations and a 3-4-fold greater chance of hospitalization compared to those without diabetes. 30% of individuals with a discharge diagnosis of diabetes will require two or more hospitalizations in any given year. Prevalence of hyperglycemia and diabetes ranging from 38% to 40% in hospitalized patients and in 70-80% of those with diabetes who have a critical illness or cardiac surgery, have been reported.

IMPACT OF HYPERGLYCEMIA IN ADMITTED PATIENTS

Hyperglycemia (as well as hypoglycemia and glucose variability) are associated with poor hospital outcomes, including prolonged hospital stay, infections, disability after discharge, readmissions, emergency department visits after discharge, higher need of transitional or nursing home care after discharge, thus leading to higher morbidity as well as mortality. Adverse outcomes are associated with the severity of hyperglycemia prior to or on admission and during hospital stay. Early identification, optimal management and prevention of hyperglycemia have direct and immediate benefits.

GLYCEMIC GOALS IN HOSPITALIZED ADULTS

The goals for initiation of treatment and subsequent maintenance, depends on the patients characteristics and severity of the illness for which the patient is admitted. Clinical status, disease severity, nutritional status, or concomitant medications that might affect glucose levels(e.g., glucocorticoids), are the factors to be considered for day-to-day decisions regarding treatment dosing.

Critically ill individuals in ICU

In critically ill individuals in ICU, for persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L) ,confirmed on two occasions within 24 h, insulin should be initiated or intensified. After initiation, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is to be maintained. However, more stringent glycemic goals of 110–140 mg/dL (6.1–7.8 mmol/L), may be maintained for selected critically ill individuals , eg post surgical, if it can be achieved without significant hypoglycemia.

Glycemic targets of > 180 mg/dL or < 110 mg/dL are not recommended in ICU patients.

Noncritically ill individuals

Majority of the noncritically ill individuals in the wards, with persistent hyperglycemia, should be treated with initiation or intensification of Insulin and/or other glucose-lowering therapies. Glycemic goal of 100–180 mg/dL (5.6–10.0 mmol/L) is recommended for these patients, but only if it can be attained without significant hypoglycemia. Same goal is recommended whether, it is newly diagnosed diabetes or stress hyperglycemia or hyperglycemia related to diabetes prior to admission.

Special populations

Higher glycemic levels up to 250 mg/dL (13.9 mmol/L) may be acceptable in special populations to treat hyperglycemia as well as avoid symptomatic hypoglycemia. In terminally ill individuals with short life expectancy, those with high risk for hypoglycemia and /or labile glycemic excursions and patients with advanced nephropathy on dialysis, treatment goals are to be kept less aggressive.

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED INDIVDIUALS

Consideration of several predictive factors for achieving glycemic goals such as, prehospitalisation therapy (OHA or insulin therapy), probable insulin resistance, HbA1c levels, duration of DM, present glycemic status and oral intake, facilitates an individualised approach.

A) Insulin Therapy

i)Critical Care Setting

Most effective method for achieving specific glycemic goals and avoiding hypoglycemia in this setting is continuous intravenous insulin infusion. Validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and immediate past and current insulin infusion rates should be used.

ii)Noncritical Care Setting

The use of subcutaneous rapid- or short-acting insulin before meals or every 4–6 hourly, if NPO or receiving continuous enteral or parenteral nutrition, is effective in these group of patients. Basal insulin or a basal plus bolus correction insulin plan is the preferred treatment for those with poor or no oral intake. An insulin plan with basal, prandial, and correction components is the preferred treatment those with adequate nutritional intake. Prolonged use of a correction or supplemental insulin without basal insulin (formerly referred to as a sliding scale) in the inpatient setting is discouraged except for noncritical with mild hyperglycemia or stress hyperglycemia.

iii)In T1DM, basal insulin with correctional dose for all hospitalized individuals, even if not taking orally, is required. Basal insulin based only on premeal glucose levels does not attain glycemic control. Prandial insulin is to be added to basal once patient

starts eating.

iv) Patient on Enteral and Parenteral Feeding:

Those on enteral feeding on basal insulin, should continue the basal dose and additional insulin for the total nutritional component should be calculated as 1unit /10-15 gm of carbohydrates in the formula feed. NPH insulin two or three times daily (every 8 or 12 h) or regular insulin every 6 hourly, with frequent adjustments made as per the composition and frequency of the feed , is effective. Correctional insulin sc 6 hourly with regular human insulin or rapid- acting insulin every 4 hourly is also an accepted regime. If enteral bolus feeding is being given, then sc regular human insulin or rapid-acting insulin (1unit/ 10–15 g of carbohydrate) before each feeding and correctional insulin added when required.

Patients on continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution (1 unit for every 10 g of dextrose), especially if preceding 24hours requirement of correctional insulin was more than 20 units.

*Use of insulin pens and insulin analogs can be continued.

*Pre mixed insulin have higher hypoglycemia events and is not recommended.

B) Non insulin therapy

T2DM individuals hospitalized with heart failure, Sodium-glucose cotransporter 2 inhibitor (SGLT2i) should be initiated or continued during hospitalization, after they recover from acute illness and upon discharge, if there are no contraindications. SGLT2i should be avoided in cases of acute severe illness in presence of ketonemia or ketonuria, and during prolonged fasting and surgical procedures. Dipeptidyl peptidase 4 inhibitors (DPP-4i) also can be continued but saxagliptin and alogliptin should be stopped in those who develop heart failure. The use of DPP-4i with or without basal insulin is a safer, simpler and effective regimen for people with mild to moderate hyperglycemia on admission (<180–200 mg/dL).

TRANSITIONING FROM INTRAVENOUS TO SUBCUTANEOUS INSULIN

Transition from continuous insulin infusion to sc insulin is started once the patient is stable and planned for transfer out from ICU. Factors to consider are stable glucose measurements for at least 4–6 hours consecutively, normal anion gap and correction of acidosis in diabetic ketoacidosis, haemodynamic stability (not on vasopressors), stable nutrition plan, and stable intravenous infusion rates. Subcutaneous basal insulin should be given 2 hours before discontinuation of infusion, to minimise rebound hyperglycemia. Dose of the combined basal and nutritional subcutaneous insulin requirements can be derived from the insulin infusion rate during the prior 6–8 hours when stable glycemic goals were achieved, preadmission insulin dose, or following a weight-based approach.

GLUCOSE MONITORING

An A1C test should be performed in all people with diabetes or hyperglycemia (random blood glucose >140 mg/dL or >7.8 mmol/L) admitted to the hospital if no A1C test result is available from the prior 3 months. It also helps to differentiate between stress- induced hyperglycemia and previously undiagnosed diabetes.

Frequency of subsequent monitoring depends on the patient's status and the insulin regimen being used.

In patients on intravenous insulin infusion, glucose monitoring ranging from every 30 minutes to every 2 hours, is preferred as it allows proper dose titration. In those who are NPO, sugar levels should be checked every 4 to 6 hourly. Those who are taking orally, pre-meals sugar should be checked (and at 3 AM in cases where there is suspicion of Dawn phenomenon or Somogyi effect).

U.S. Food and Drug Administration (FDA) approved

Point of Care (POC) hospital-calibrated glucose monitoring systems should be used for hospital blood glucose monitoring. They provide adequate information with rapidity, simple to use and point of care advantage. Though they are not as accurate or as precise as laboratory glucose analysers but are very essential for management of hospitalised patients. It uses capillary blood glucose, the result of which due to low perfusion, oedema, anaemia or erythrocytosis, maybe compromised sometimes. However, the accuracy, precision, and interference of these monitors are to be balanced with the clinical requirements. Any result by monitor which does not corroborate with the clinical status of the patient, should be repeated and then confirmed by measuring a sample in the clinical laboratory. Blood sugar levels in asymptomatic hypoglycaemic events should always be cross checked in the lab.

Continuous Glucose Monitoring

The use of CGM should be continued in those using a personal continuous glucose monitoring (CGM) device (insulin pump or automated insulin delivery.) if they can operate their devices safely and independently when proper oversight supervision is available during hospitalization. Clinical appropriateness, with confirmatory POC measurements should guide insulin dosing decisions and confirm hypoglycemia. Ensuring availability of necessary supplies, resources, training, expertise and institutional protocols related to implementation of diabetes technology is a requisite.

HYPERGLYCEMIA AND GLUCOCORTICOID THERAPY

The prevalence of concomitant glucocorticoid therapy in hospitalized individuals is 10–15%, and steroid induced hyperglycemia, with its associated increased morbidity and mortality, can result in 56–86% of individuals with and without preexisting diabetes. Appropriate insulin treatment depends on the type and duration of action of the glucocorticoids.

For those receiving daily oral intermediate-acting glucocorticoids (prednisone or prednisolone), have peak plasma levels in 4–6 hours, usually have a normal or mild fasting hyperglycemia, with increasing hyperglycemia in afternoon, and highest in the evening. NPH insulin (alone or in addition to basal bolus or OHA) administered concomitantly with intermediate-acting steroids is recommended as its peak matches with the steroid induced hyperglycemic response.

Long-acting basal insulin are recommended for long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use. Prandial and correctional insulin are used in addition for higher doses of glucocorticoids. POC glucose monitoring and adjustment of insulin based on the revision of the steroid therapy must be done to reduce both hyperglycemia and hypoglycemia.

PERIOPERATIVE CARE

Approximately 20% of patients undergoing surgery have DM and 23–60% have undiagnosed diabetes or prediabetes. Surgical stress and counterregulatory hormone release further enhance the risk of hyperglycemia. Approach focusing on the following points helps in mitigating the composite complications:

1.In diabetics at high risk for ischemic heart disease, having autonomic neuropathy or renal failure, a detailed preoperative assessment to be performed.

2.Hb A1C of less than 8% (<64.0 mmol/L) for elective surgeries is preferred.

3.Blood glucose goal in the perioperative period should be between 100–180 mg/ dL (5.6–10.0 mmol/L) (126) within 4 h of the surgery. (129) Stricter goals have no benefit and are associated with increased hypoglycemia.

4.SGLT2i should be discontinued 3–4 days and weekly dose GLP -1 RA at least 7 days prior to surgery. OHAs should be held on the morning of surgery.

5.NPH insulin should be reduced to half the dose and

analogs decreased by 75–80%. 25% reduction of basal insulin dose given in the evening before surgery.

6.Blood glucose monitoring 4 -6 hourly till patient is NPO and short- or rapid-acting insulin as needed.

7. Basal-bolus insulin with correctional dose in immediate post op period reduces postoperative wound infection, pneumonia, bacteraemia, and acute renal and respiratory failure.

DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE

There is considerable variability in the presentation of DKA and HHS in hospitalised patient and so the standard protocol requires customisation depending on the clinical presentation and co morbidities.

PREVENTION OF HYPOGLYCEMIA

Hypoglycemia is a severe consequence of deranged metabolism and of diabetes treatment and should be minimized during hospitalization as it increases mortality. Identification, treatment and prevention of hypoglycemia is important. In addition to Iatrogenic hypoglycemia due to insulin dosing errors, missed doses, administration errors , improper combination with OHA , failed dose adjustment in renal failure, other factors like reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short or rapid-acting insulin doses in relation to meals, reduced infusion rate of intravenous dextrose, interruption of artificial feeds, delayed or missed blood glucose checks, altered ability of the individual to report symptoms and inappropriate management and follow-up of the first episode of hypoglycemia should be addressed.

FUTURE PROSPECTS AND RESEARCH AREAS

Customised, simplified, effective and safe therapy focussing on specific glycemic goals and settings requires further research. Development of structured order sets that provide computerized guidance for glycemic management. Insulin requirements during hospitalization can be predicted using Machine learning and EMR data developed algorithms. Integration of technology like closed loop system (artificial pancreas) or automated insulin delivery systems with the EMR and analysis of the cost effectiveness and interoperability of these technologies, can improve the hyperglycemia management in hospitalised patients.

CONCLUSION

Hyperglycemia in hospital is frequent and is associated with adverse outcomes. An individualised approach is most beneficial. In presence of co morbidities, team approach with all relevant specialists, yields best control of the glycemic status as well as of the underlying diseases.

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Chapter 33

Monitoring and Management of Diabetes in Dialysis

Iain Charles Pearson Cranston

INTRODUCTION

The role of glucose control in individuals requiring renal replacement therapy has long been debated. Whilst 'tight' control has been validated in preventing the development of renal disease, its role in the management of those in whom renal disease has already developed has a far less clear evidence-based and the risks related to hypoglycaemia in those on maintenance haemodialysis are well recognised. For some years this has resulted in a state of 'therapeutic nihilism' around glycaemia management in those with advanced renal disease (esp. those on renal replacement therapies), despite the fact that at least 2 large studies have identified increased rates (at least 2X) of morbidity and mortality in people with diabetes on haemodialysis with higher (either >8% or >10%) levels of glycaemic control compared to those with tighter control (HbA1c 6-7%).

BACKGROUND

It is widely believed that there is a "U shaped" risk curve in relation to diabetes control in this group with optimal control being defined as 6.5 – 7.5% (despite the fact that interpretation of HbA1c in this population is fought with difficulties itself due to the impact of anaemia, iron stores and renal disease on the HbA1c independent of the glycaemic experience!). Several other markers of glycaemia rather than HbA1c have been suggested in this population group (Fructosamine and Glycated Albumin predominantly) – although these too suffer from condition-related inaccuracies in a similar way to HbA1c. Thus, as we now live and work in an environment where direct measurements of glucose experience are now routinely employed in the clinical care of individuals with diabetes it seems obvious that it is to these measures (essentially CGM) that we should now turn in order to help guide the challenging issues around glycaemic management in this population group. Many of the standard therapeutic options in the management of diabetes are either relatively or absolutely contra-indicated in those with ESRF, creating a relatively more 'insulin-centric' approach in this group. Add to this the reduced / altered symptom-complex for hypoglycaemia, the glycaemic impact of dialysis itself (usually against a 10mM glucose solution in haemodialysis), and the variable effects of dialysis on clearance of diabetes therapeutic molecules (e.g. insulin and sulphonylureas), with cyclical uraemia / acidaemia and hyperphosphatemia which can impact both insulin sensitivity and (in those with retained pancreatic function) insulin secretion, this group indeed present therapeutic challenges which require close monitoring for effective manipulation of therapeutic agents.

Whilst (observationally) it is the case that of those with T2D who develop ESRF approx. 2/3 will require progressively less diabetes therapy as they approach end stage disease, (often, probably inaccurately, described as 'burnt-out' diabetes) for those with type

1 diabetes and the remaining third, effective glycaemic management decisions are thus potentially critical. For those patients undergoing haemodialysis in centre, the commonest dialysis regimen is a 3-session per week strategy of 3-4 hours dialysis at a time, which results in falling glucose during the session with very erratic levels in the first 6-8 hours after (depending on the balance between dialysis related clearance and therapy timings). Post dialysis hypo and hyper-glycaemia are well-described and represent a 'clear and present danger' for people with diabetes so treated – in particular these post-dialysis glycaemic swings have been associated with sudden death, MI and CVA episodes.

Although SMBG is potentially an important tool, the burden of disease (along with ischaemic risks associated with brachial fistulae) limit its uptake and effective implementation. By contrast CGM is well-tolerated (generally advised in the non-fistula arm) and a number of recent validation studies (at least for Dexcom and Abbott sensors) have confirmed its accuracy in this population group, as not significantly different from the general population.

Given the risks for this group, regular CGM should be made available relatively routinely therefore for anyone on dialysis who is using insulin, and for others, given the challenges in glycaemic assessment with standard measures, periodic diagnostic sensor applications should be considered every 3 – 6 – or 12 months depending on the perceived risk for the individual.

UK-Based recommendations on glycaemia management in this population group (ABCD / Renal Association) conform to the following hierarchy

1. Avoidance of ALL severe hypoglycaemia (requiring 3rd party assistance)
2. Avoidance of significant hypoglycaemia (significant = < 3.0 mmol/L)
3. Minimisation of time spent with glucose < 3.9 mmol/L (<1% or 15mins per day)
4. Minimisation of time spent with glucose > 13.9 mmol/L
5. Minimisation of excessive glycaemic variability (CV>36% or SD >3.5mmol/L)

From a more general perspective, given the high-risk nature of this group, it is appropriate to 'target set' using the international consensus guidance of 50% time in range and <1% below, although for some (especially those being prepared for transplantation) a more aggressive target -set might be appropriate

RECOMMENDATIONS

A structured approach to risk stratification can guide the appropriate use of CGM to optimise safety and efficacy.

1. Permanent CGM

- Recommend for all people on dialysis with T1D
- Recommend for all people on dialysis with T2D on multiple daily insulin injections (>2 per day) and/or recurrent severe hypoglycaemia, impaired awareness of hypoglycaemia, a condition or disability that means they cannot self-monitor their blood glucose using capillary blood glucose monitoring, would otherwise be advised to self-measure at least 8 times a day.

This aligns with NICE NG17 and NG28 guidance, which supports CGM for adults and children with T1D, and select individuals with T2D.

2. Intermittent CGM (High-Risk Groups)

For individuals at high risk of hypoglycaemia on basal-only regimens, intermittent CGM use provides valuable data for proactive management.

Consider in people who:

- Are using basal insulin and have variable appetite or dialysis-related glucose swings
- Have impaired hypoglycaemia awareness

- Are transitioning between therapies or dialysis modalities

Frequency: Intermittent use for 10-14 days every 6-12 months or as clinically indicated.

3. Diagnostic CGM (Short-term Use)

Used where the glycaemic pattern is unclear or HbA1c is unreliable due to advanced CKD or treatment with erythropoiesis-stimulating agents. Diagnostic CGM is particularly useful to:

- Identify unrecognized hypoglycaemia or hyperglycaemia
- Assess glycaemic variability around dialysis sessions to inform insulin titration and guide treatment plans

MONITORING STRATEGY AND CONCLUDING REMARKS

- Review CGM data regularly at each consultation, including time below/above range, time in range and glucose variability.
- Focus review on dialysis days and post-dialysis periods, when the risk of delayed or progressive hypoglycaemia is highest.
- Adjust targets based on clinical context, dialysis schedule, and risk profile.
- Combine CGM data with clinical review, including dietary patterns, insulin use, and symptoms.

During the presentation at this meeting, case-based clinical care around these principles will be presented, focussing on individualisation of care across a dialysis cycle. In particular, insulin adjustment across the cycle may be a key part of educational insulin use in this group, with early evidence suggesting that automated insulin delivery may (in T1D patients at least) represent a useful option.

Automated insulin delivery (AID) systems—also known as hybrid closed-loop (HCL) systems—combine a continuous glucose monitor (CGM), an insulin pump, and a control algorithm that adjusts insulin delivery in real time based on glucose levels. They reduce the burden of frequent insulin dose adjustments and help maintain glucose within target range. Use of these systems is increasing in people with type 1 diabetes, supported by NICE guidance.

Their use in people with type 1 diabetes on dialysis is emerging but remains an area of limited evidence. Small case series have reported improved time in range and reduced hypoglycaemia, including during and after dialysis sessions. In a single-centre case series of four individuals with longstanding T1D and ESKD on thrice-weekly haemodialysis, significant improvement in time in range was observed (pre-HCL 43.5% vs post-HCL 64.8%; p=0.015), and a reduction in time above range (pre-HCL 55.5% vs post-HCL 34.8%; p=0.03) over a mean follow-up of 4.5 months.

Currently no commercially available HCL system is licensed for use during dialysis. Its use therefore needs to be closely monitored, as it is unclear whether the HCL algorithms are safely able to adapt to rapid changes in glucose. There are also inherent challenges in this complex cohort which include frailty, visual impairment and reduced manual dexterity to self-manage. Where HCL systems are used, recommendations include:

- Adjust treatment targets and active insulin time settings to more conservative parameters when initiating dialysis or commencing on HCL in the context of ESKD.
- Avoid bolus dosing during dialysis to mitigate against hypoglycaemia.
- During dialysis, if concerns of hypoglycaemia, temporary activity/ exercise/ sleep mode may be activated to allow for a higher glucose target.

DISCLAIMER

This paper is based on the UK National Guidelines Section for the monitoring and management of diabetes in Dialysis patients – a combined commission from the Association of British Clinical Diabetologists (ABCD) and the Renal Association (RA) of which Dr. Cranston and Dr. Avari are the authors.

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Chapter 34

In and After Care of Hypoglycaemia

Santosh Adhikari

INTRODUCTION

Iatrogenic hypoglycaemia is the most important limiting factor in glycaemic management of diabetes. It causes recurrent morbidity in most people with Type 1 diabetes mellitus (T1DM) and many with Type 2 diabetes mellitus (T2DM) and is sometimes fatal. The key physiologic defences against falling plasma glucose concentrations are decrements in insulin and increments in glucagon and epinephrine. The behavioural defence is carbohydrate ingestion prompted by symptoms that are largely the result of sympathetic neural activation. Hypoglycaemia is a barrier to reaching the safe and desired glycaemic goals in patients with diabetes mellitus (DM).

DEFINITION

Hypoglycaemia, or low blood glucose, in an adult is a clinical state associated with low (less than 70mg/dl) as per the American Diabetes Association (ADA) Standards of Care 2019. Relatively low plasma glucose concentration is usually associated with signs and symptoms of autonomic hyperactivity, and neuroglycopenia is also encountered.

CLASSIFICATION OF HYPOGLYCEMIA

Level 1 - Alert value of plasma glucose (less than 70 mg/dl)

Level 2 - Serious biochemical hypoglycaemia with plasma glucose less than 50mg/dl

Level 3 - Severe hypoglycaemia, where the patient has impaired cognitive function and requires external help to recover. In non-severe hypoglycaemia, the patient has symptoms but can self-treat and cognitive functions be mildly impaired.

MORTALITY AND MORBIDITY IN HYPOGLYCEMIA

Delay in treatment can result in profound sequelae, including death. The risk of permanent neurological deficit increases with prolonged hypoglycaemia. Such deficits can include hemiplegia, memory impairment, diminished language skills, decreased abstract thinking, and ataxia. Acute sequelae include coma, cardiac dysrhythmia and death. Because the consequences of hypoglycaemia can be devastating, and an antidote is readily available, diagnosis and treatment must be rapid in any patient with suspected hypoglycaemia, regardless of the cause

RISK FACTORS FOR SEVERE HYPOGLYCEMIA ARE LISTED BELOW:

- Strict glycaemic control
- Impaired awareness of hypoglycaemia
- Age (very young & elderly)
- Long duration of diabetes
- Sleep
- C-peptide negativity (indicating complete insulin deficiency)
- History of previous severe hypoglycaemia
- Renal impairment
- Genetic, e.g., angiotensin-converting enzyme (ACE) genotype.

CAUSES OF HYPOGLYCEMIA IN DIABETES

Common causes of hypoglycaemia	Other causes of hypoglycaemia in non-diabetic and in patients with diabetes
• Missed, delayed or inadequate meal • Unexpected or unusual exercise • Alcohol • Errors in oral anti-diabetic agents or insulin dose/schedule/administration • Poorly designed insulin regimen, particularly if predisposing to nocturnal hypoglycaemia • Lipo-hypertrophy at injection sites, causing variable insulin absorption • Gastroparesis due to autonomic neuropathy, causing variable carbohydrate absorption • Malabsorption, e.g., coeliac disease • Unrecognised other endocrine disorder, e.g. Addison's disease • Factitious (deliberately induced) • Breastfeeding	• GI surgery (especially gastric surgery) • Islet cell Tumour/Extra-pancreatic tumour (Rare) • Hypopituitarism • Adrenal insufficiency • Sepsis • Starvation/lack of appropriate intake

Hypoglycaemia-associated autonomic failure (HAAF)

Unfortunately, a prior incident of hypoglycaemia blunts the autonomic nervous system (norepinephrine and epinephrine), neuroendocrine (glucagon, Cortisol and growth hormone) and metabolic (endogenous glucose production) counter-regulatory responses to subsequent episodes of hypoglycaemia in T1DM, T2DM on intensive control and also in healthy persons. The blunting can occur within a few hours and last up to 5 days.

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

The organ systems that manifest the signs and symptoms of hypoglycaemia are thecentral and autonomic nervous systems. The brain is one of the first organs affectedby lowered blood glucose levels. Neurons in the hypothalamus detect falling glucoselevels and respond by increasing autonomic drive to the periphery. Catecholamines,glucagon and insulin changes are the initial response to hypoglycaemia. Cortisol andgrowth hormone plays a role in hypoglycaemia for longer than 2 hours.

MOST COMMON SYMPTOMS OF HYPOGLYCEMIA

The Symptoms can be divided into three headings:

Autonomic	Neuroglycopenic	Non-Specific
• Sweating • Trembling • Pounding heart • Hunger • Anxiety	• Confusion • Drowsiness • Speech difficulty • Inability to concentrate • Incorporation • Irritability and anger	• Nausea • Tiredness • Headache

SIGNS OF HYPOGLYCEMIA

- Pulse rate - Increases
- Pulse volume - Full
- Temperature - Maybe decreased
- Respiration - Shallow or normal
- Blood pressure - Normal
- Skin - Clammy, sweating
- Tongue - Moist
- Tissue Turgor - Normal
- Eyeball Tension - Normal
- Breath - No acetone (Normal)
- Reflexes - Brisk

LABORATORY TESTS

Plasma glucose in low - Less than 70 mg/dl

Urine glucose is negative to positive, depending on the timing of the last voiding Blood pH is normal, and plasma acetone and bicarbonate are normal.

MANAGEMENT OF HYPOGLYCEMIA

Care for a hypoglycaemic attack involves immediate treatment to raise blood sugar levels, followed by guidance to stabilize glucose and prevent future episodes.

The specific approach depends on the severity of the attack and whether the person is conscious or not.

TREATMENT PLAN FOR CONSCIOUS PERSON (MILD TO MODERATE HYPOGLYCEMIA)

Following the "15–15 rule" is recommended by the American Diabetes Association (ADA). Patients who are alert are given 15 grams of glucose or carbohydrate. It is expected that plasma glucose should rise by 15 minutes. Glucose check is repeated every 15 minutes and if necessary, 15 grams of glucose or carbohydrate is repeated till blood glucose level comes above 70 mg/dl or above. Once the plasma glucose level comes above 70 mg/dl, then the patient is asked to eat a meal containing good amount of carbohydrate (polysaccharide) to maintain the blood glucose level in euglycemic status.

While choosing oral fast-acting carbohydrate, we can use glucose drink, glucose tablets (15–20gm), and fruit juices (not for chronic kidney disease patients). Most commonly used item is sugar which is easily available. In this case, taking 3 teaspoons sugar dissolved in water may be a suitable option. Patients on α-glucosidase inhibitors should use glucose powder (instead of sugar) as they cannot breakdown sugar easily.

TREATMENT PLAN FOR UNCONSCIOUS PERSON WITH HYPOGLYCEMIA (SEVERE HYPOGLYCEMIA)

People with severe hypoglycaemia may be unconscious and unable to swallow. In this case, oral glucose must be avoided due to the risk of aspiration. Instead, an intramuscular injection of glucagon (1 mg in adults and 0.5 mg in children) should be given by a relative or friend who is aware of the hypoglycaemic risk of the patient and prepared to administer treatment.

Following recovery of consciousness, carbohydrates should be ingested.

Alternatively, in cases of severe hypoglycaemia with coma or seizures, intravenous glucose (80–120 ml of 20% solution, i.e., 16–24 grams of glucose) can be given over 10-15 minutes and repeated until recovery of consciousness. This should be followed by a continuous infusion of glucose at the rate of 60–80 ml/hour until glucose levels are stable and the patient is able to eat. The history of the precipitating cause of hypoglycaemia must be ascertained, and future course of action chalked out to prevent further episodes. The treatment of reactive hypoglycaemia of fed-state includes correction of dietary habits. Frequent small snacks are advised in nonspecific reactive hypoglycaemia; the diet should contain some slowly absorbable carbohydrates and more

protein. Alcohol-induced hypoglycaemia is prevented by reducing alcohol intake and increasing the ingestion of food.

AFTERCARE OF HYPOGLYCEMIA

Once the blood glucose level comes back to the target range (e.g., above 70 mg/dl), the patient is advised to take a balanced snack or meal with protein and carbohydrates to keep it stable and prevent a subsequent drop in blood glucose. Monitoring blood glucose for a couple of hours is necessary to ensure it stays stable. Self-monitoring of blood glucose (SMBG) is very helpful in this regard. A patient recovering from hypoglycaemia is advised to avoid strenuous physical activity for at least 24 hours, so that further hypoglycaemia may be prevented. Documentation of the hypoglycaemic event is very important. We should note when it happened, the circumstances, and what was eaten by the patient prior to the attack to help to identify patterns and prevent future episodes.

We also need to review the meal plan, exercise pattern and adjust the medications to prevent future attacks of hypoglycaemia.

STRATEGIES TO PREVENT HYPOGLYCEMIA

1. Patients must be counselled about the causes and early signs and symptoms of hypoglycaemia. General outpatient diabetic education or inpatient diabetic teaching is indicated.
2. Caregivers should receive education in recognition and response to early signs and symptoms of hypoglycaemia.
3. Optimization of insulin or oral therapy to suit the patient's lifestyle should be Done.
4. Use of rapid-acting insulin analogues with long-acting insulin analogues in Type 1 diabetes mellitus is important.
5. Some long-acting older sulfonylureas should be shifted to short-acting sulfonylureas as modified-release gliclazide.
6. Shifting to a basal-bolus therapy from a premix regimen may be helpful.
7. Frequent glucose monitoring is important in patients with hypoglycaemic unawareness.
8. SMBG (Self-Monitoring of Blood Glucose) is very helpful in this regard.
9. Caution is needed when risk factors (exercise, age, ethanol consumption) are encountered.
10. Patients should have an ID tag stating that he/she is diabetic, and it should be worn in a visible place with important information.

CONCLUSIONS

Hypoglycaemia continues to be the rate limiting step of intensive treatment of diabetes with insulin and sulphonylureas. Symptoms of hypoglycaemia can be subtle to alarming, but tend to be same in a given individual. Hypoglycaemic unawareness occurs in diabetics with very tight glycaemic control. Hypoglycaemia can be frightening and when severe, produce cognitive impairment and occasionally cardiac arrhythmia and acute autonomic failure. When occurring frequently in a patient, the hypoglycaemic targets must be relaxed.

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Chapter 35

In Patient Management of Acute Metabolic Complications of Diabetes

Brajendra Lahkar

INTRODUCTION

Diabetic ketoacidosis, Hyperglycaemic hyperosmolar state, Lactic acidosis, and Hypoglycaemia are the most significant acute metabolic complication of Diabetes Mellitus leading to excess mortality and morbidity. Most of these dysglycaemic events occur due to missed doses of insulin or oral antidiabetic drugs, missed meals infections, other stress such as acute myocardial infarction, pancreatitis or due to drugs which may be the cause of hyperglycaemia (eg. Steroids) or hypoglycaemia (eg. Gatifloxacin or Quinine). Quick recognition of these complication and prompt treatment save many lives. This article will discuss in brief, the recognition, and principles of management of these acute metabolic complications in hospital.

DIABETIC KETOACIDOSIS (DKA)

DKA is common & life-threatening complication of Type1Diabetes particularly at diagnosis and less common in Type 2 Diabetes. Insulin deficiency, increased insulin counter-regulatory hormones (cortisol, glucagon, growth hormone and catecholamines) and peripheral insulin resistance leading to hyperglycaemia, dehydration, ketosis, and electrolyte imbalance are the hallmark pathophysiologic features of DKA.

The American Diabetes Association (ADA), the International Society for Paediatric and Adolescent Diabetes jointly agreed to define DKA as triad of the following:

1. hyperglycaemia, i.e., plasma glucose >250 mg/dL (>13.88 mmol/L)
2. venous pH <7.3 and/or bicarbonate <15 mmol/L
3. moderate or large ketone levels in urine or blood.

Management of DKA

All DKA patients should be admitted in Intensive Care Units (ICU).

A. Start **initial Resuscitation**:

1. Airway & breathing: Endotracheal Intubation to be considered if patient's sensorium is low and Glasgow coma scale (GCS) is ≤ 8. Ventilation to be assisted with usual volume control mode and with usual settings used for non-ARDS patients.
2. Circulation: Two large bore Intravenous catheters to be inserted urgently. In severe hypovolemia peripheral veins may be collapsed and then a central venous line to be secured urgently.

Blood should be drawn for following initial essential investigations

Metabolic panel including electrolytes, BUN, Creatinine, Arterial blood gas, complete blood counts, serum ketones. Other essential tests are Urine analysis and ketones by dipstick, ECG, Chest X-Ray, Screening for infective foci.

B. **Fluid therapy** is the most essential step in resuscitation as these patients are severely hypovolemic, tissue perfusion is at stake and they deteriorate very fast. Crystalloid such as isotonic (0.9%) saline or balanced crystalloids at 1Litre/hour to be initiated. Subsequent fluid therapy is to be guided by the volume status and cardiac reserve of the patient.

If patient is having severe hypovolemia, 0.9% saline or buffered crystalloids to be given at 15-20ml/kg/hour initially and then rate can be reduced to 4-14ml/kg/hr. In mild hypovolemia, rate of infusion should be less and based on clinical assessment. If initial blood sugar is ≤ 250mg/dl, 5% Dextrose containing fluid to be added. In patients with cardiogenic shock, vasopressor may be needed early along with haemodynamic monitoring. Volume deficit to be corrected within 24 hours and subsequent volume replacement is based on serum Sodium (Na^+) level. If Sodium is high or normal, 0.45% saline at approximately 250-500ml/kg/hr to be infused. If sodium is low, 0.9% saline at same dose is to be infused [3].

C. Electrolyte abnormalities (most importantly **serum Potassium**) to be corrected swiftly. Adequate kidney function is to be ensured (urine output ≥ 50ml/hr) before correcting potassium supplementation[3].

If serum K^+ < 3.5 mEq/Lt, then Inj Potassium Chloride (KCL)at 10-20 mEq/Lt to be infused and Insulin therapy should be delayed till serum K^+ is >3.5mEq/Lt.

If K^+ is 3.5-5mEq/Lt the add 10-20mEq of Inj KCL in each litre of IV fluid infused to maintain K^+ level in between 4 – 5mEq/Lt.

If K^+ is >5mEq/Lt, Potassium supplementation is not to be given, but serum K^+ to be monitored every 2 hours.

D. **Insulin Therapy**: Initiation of Insulin therapy to be delayed if serum K^+ level is <3.5mEq/Lt. Regular insulin at 0.1 unit/kg/hr as infusion to be initiated through an infusion pump. If pump is not immediately available, a bolus dose of 0.1 unit/kg of regular insulin to be given immediately. If serum blood sugar does not fall by at least 50-70mg/dl, dose of Insulin infusion/hour to be doubled. In less severe cases and after volume replacement, insulin at same doses can be given subcutaneously also if infusion pump is not available[3]. When serum glucose level reaches <250mg/dl, insulin infusion to be reduced to 0.05 unit/kg/hr infusion or 0.05 unit/kg subcutaneously every 2 hours and maintain serum glucose in 150-200 mg/dl range till DKA resolves. Once patient becomes stable, IV insulin to be changed to subcutaneous insulin therapy based on protocol followed in the units. Usually iv infusion is stopped 2 hours after initiation of subcutaneous insulin therapy

E. **Correction of acidosis**: Need for bicarbonate therapy to be assessed. If pH is <7, then 100mEq of $NaHCO_3$ to be mixed with 400ml sterile water for injection and to be infused over 2 hours. Repeat the dose every 2 hours till pH reaches >7. In case pH is >7, no bicarbonate therapy is recommended [3].

F. **Precipitating factors to be identified and treatment to be initiated.** Missed insulin doses, Infections, Trauma, Myocardial infarction, Pancreatitis, Pregnancy, CVA, steroid use etc should be identified and treated.

HYPERGLYCAEMIC HYPEROSMOLAR STATE (HHS)

HHS is defined as extreme elevation in blood glucose >600 mg/dL (>33.30 mmol/L) and serum osmolality >320 mOsm/kg in the absence of significant ketosis and acidosis. Small amounts of ketones may be present in blood and urine [4]. It is less common than DKA and accounts for <1% of all admission due to Diabetes and up to 4% of newly diagnosed Type2 Diabetes. It is more prevalent in elderly with lots of comorbidities.

The usual precipitating factors are dehydration, medications such as steroids and thiazides, acute illness, Cerebro-vascular disease, advanced age.

supplementation are same as that has been described above for DKA.

In patients with HHS, fluid and insulin therapy should be titrated to achieve the following goals:

- Decline in serum glucose level ≤90 to 120 mg/dL (5 to 6.7 mmol/L) per hour
- Decline in serum sodium ≤10 mmol/L in 24 hours
- Decline in Plasma osmolality ≤3 to 8 mOsm/kg per hour.

Complications of HHS treatment are Hypoglycaemia, Hypokalaemia, cerebral oedema, hyperchloremic acidosis and non-cardiogenic pulmonary oedema.

Following are the main differences between DKA and HHS (Table 1)

	DKA	HHS
Glucose	250- 600 mg/dl	Often >900mg/dl
Ketoacidosis	Profound	Minimal or none
HCO_3	<15mEq/Lt	>15mEq/Lt
Osmolality	300-325 mOsm	often > 350mOsm
Insulin level	very low / none	may be normal
Age	Young	Elderly
Onset	Acute, over hours todays	Chronic, days to weeks
Associted disease	Uncommon	Common
Seizure	very rare	Common
Coma	Rare	Common
Dehydaration	Severe	Profound
Mortality	0-10%	20-40%

Management of HHS

Treatment of HHS is like that in DKA if not complicated by underlying conditions. IV fluids and Insulin therapy promptly reverses the condition.

Initial evaluation of cardiovascular, respiratory, renal and mental status should be prompt. Initial resuscitative measures are same as that for DKA.

Fluid therapy, Insulin therapy, Potassium

HHS is considered resolved when all the following criteria are met:

- Calculated effective Plasma osmolality is <300 mOsmol/kg
- Serum glucose is <250 mg/dL.
- Urine output is >0.5 mL/kg per hour
- Cognitive status has returned to baseline

Lactic acidosis (LA)

LA consists of elevation of lactic acid above >2.2mmol/L with acidosis (pH <7.3) and without ketoacidosis. There may be low levels of ketones present (1:4 on serum dilution or β-OHB >0.4–<0.6 mmol/L).

LA is uncommon complication of Diabetes. The frequency of hospitalizations due to LA is 1.2% among patients with diabetes and 1.0% among those without diabetes. Mortality is high with higher lactate level with acidosis. Usual precipitating factors for Lactic acidosis are impaired tissue oxygenation such as hypoxaemia, shock, sepsis, carbon monoxide poisoning, Phenformin use (though it has been discarded option). Though initial reports implicated metformin as precipitating factor for LA specially in renally impaired cases, a Cochrane review found that the incidence of metformin-associated LA was 8.4 cases per 100,000 patient-years, and in the non-metformin group, it was 9 cases per 100,000 patient-years [6].

The effective treatment of LA is to improve tissue oxygenation by improving tissue perfusion by means of volume replacement, reversing shock state, improving myocardial dysfunction, and controlling sepsis and correction of hyperglycaemia.

Hypoglycaemia

The American Diabetes Association Workgroup on Hypoglycaemia defined hypoglycaemia broadly as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm

Though clinical classification of Hypoglycaemia is useful for tracking, various societies agree upon classification of three levels of hypoglycaemia [7].

Level 1 Hypoglycaemia is a blood glucose level <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3 mmol/L) should alert the patient to act.

Level 2 Hypoglycaemia is a blood glucose level <54 mg/dL (3 mmol/L) indicates serious hypoglycaemia requiring immediate action.

Level 3 Hypoglycaemia is defined as a hypoglycaemic event that requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose level may not be available at that time.

Management: All suspected level 2 & 3 hypoglycaemic patients are to be admitted in ICU.

Prompt recognition of hypoglycaemia: Clinical features can be due to sympathetic activation such as diaphoresis, tremor, anxiety, palpitation, hunger, paraesthesia, tachycardia. These features may be masked due to treatment with betablocker or autonomic neuropathy. In some, neuroglycopenic features such as drowsiness, behavioural abnormality, seizure, and coma may predominate [5].

Simultaneously both capillary and venous Blood glucose to be checked immediately.

Airway, breathing and circulation (ABC) must be stabilized as initial resuscitation.

Intra-venous Dextrose 50ml of 25-50% Glucose to be infused rapidly. Repeat the infusion till blood glucose level improves to >70mg/dl and patient become asymptomatic. Intravenous glucose infusion for 6 hours to be started if risk of prolong hypoglycaemia is high such as in CKD patients, those who are on Long-acting insulin, oral antidiabetic drugs.

Inj Glucagon at 1 mg SC or IM and **Inj Octreotide** at 25-50 microgram SC is considered if hypoglycaemia is suspected to be resistant and severe.

Precipitating factors to be identified and corrected along with general measures. Common factors are missed meals, inadequate meals, Insulin overdose, change of therapy, concomitant use of hypoglycaemic drugs, hepatic failure and renal failure. One should also look for other drugs which may cause hypoglycaemia such as Gatifloxacin, Artesunate, Lithium, Propoxyphene, Quinine, etc.

CONCLUSION

Acute metabolic complications are preventable and treatable complications of Diabetes. If delayed in recognition and treatment, it may lead to

unacceptably high excess mortality and morbidity in Diabetes. Prompt treatment based on simple algorithm, which can be followed anywhere, can save many lives.

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Section 11

Section Editor : **Dinesh Agarwal & Swapnav Borthakur**

Diabetes, Obesity and Incretin Mimetics

Chapter 36

Cardiovascular-kidney-metabolic (CKM) syndrome and type 2 diabetes

Avik Chakraborty

INTRODUCTION

Cardiovascular-kidney-metabolic (CKM) syndrome is a paradigm-shifting model in contemporary medicine that interlaces the interconnectedness of cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders like type 2 diabetes (T2D). The American Heart Association (AHA) introduced the syndrome in 2023, which highlights an integrative strategy to combat the increasing global burden of these connected conditions. With approximately 700 million people impacted by CKD or CVD and more than 529 million diagnosed with diabetes—mostly T2D—CKM syndrome identifies a critical public health issue that disproportionately affects marginalized groups. The syndrome's identification results from the increasing body of evidence that such diseases do not act independently but instead cross-impact one another through common risk factors and pathophysiological pathways. To date, the need to address CKM is heightened by increasing rates of prevalence and ongoing disparities, requiring integrated strategies for prevention, screening, and management.

DEFINITION AND CLASSIFICATION

CKM syndrome has been described as a complex condition involving the interrelatedness of CVD, T2D, and CKD, representing their common aetiology and reciprocal exacerbation. It incorporates more than overt disease states to cover those at risk through metabolic derangements, early renal impairment, or cardiovascular predispositions. The AHA's 2023 presidential advisory recasts this interaction, heretofore referred to as cardiovascular-renal-metabolic (CRM) syndrome, as CKM to highlight a global approach to organ-system interaction. The classification system, a foundation for CKM management, categorizes the disease into four stages to inform clinical decision-making and the timing of intervention:

Stage 0: Symbols the lack of CKM risk factors, and the goal is primordial prevention in order to promote maximum health with lifestyle and environmental changes. This stage aims at persons with no traceable adiposity problem or metabolic disturbance.

Stage 1: Characterized by excess or dysfunctional adiposity—e.g., central obesity, increased waist circumference, or dysfunctional fat distribution—without a finding of subclinical or clinical organ damage. It is an early warning stage where intervention can prevent further advancement.

Stage 2: Encompasses the appearance of known metabolic risk factors (such as hypertension, dyslipidaemia, hyperglycaemia) or mild to moderate CKD (such as eGFR 60-89 mL/min/1.73 m^2 with microalbuminuria). This stage signifies that there should be targeted risk factor management.

Stage 3: Includes subclinical CVD, i.e., coronary artery calcium scores or early markers of heart failure (e.g., increased NT-proBNP), together with

continued CKM risk. It is a transitional stage that needs increased monitoring and treatment.

Stage 4: Includes clinical CVD (e.g., myocardial infarction, heart failure, stroke) or CKD advanced stages (e.g., KDIGO stage 4, eGFR <30 mL/min/1.73 m^2), which requires guideline-based treatment for established disease.

This staged model allows for early recognition and specific interventions, recognizing the gradual progression of CKM and the possibility of progression from risk factors to life-threatening disease.

EPIDEMIOLOGY

The epidemiological context of CKM syndrome demonstrates its extensive reach and increasing burden. Prevalence from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2020 show that about 25% of U.S. adults show at least one CKM condition, of which 8% show overlaps between two or more conditions. The prevalence grows dramatically with age, reaching 25% in adults aged 65 and older, highlighting the age-related increase in susceptibility to disease. Worldwide, the numbers are overwhelming: more than 700 million have CKD or CVD, and the diabetes pandemic includes 529 million, of whom 96% have T2D. Comorbidities are dramatic—nearly one-third of T2D patients also have CVD, 40% struggle with CKD, and 20-40% of heart failure presents with T2D. The COVID-19 pandemic worsened the trend, reversing pre-pandemic declines in CVD mortality and maintaining high death rates through to 2025. Additionally, the interaction of social determinants of health (SDOH) including restricted healthcare access, food insecurity, and educational inequalities enhances susceptibility, especially among minority groups where comorbidity loads are inordinately elevated. This epidemiologic profile highlights the imperative to initiate targeted public health programs to stem the rising tide of CKM syndrome.

PATHOPHYSIOLOGY

The pathophysiologic mechanism of CKM syndrome is a dynamic process based on the interaction of renal impairment, metabolic dysregulation, and cardiovascular deterioration, with defective adipose tissue as the key driver. Excess or ectopic fat, especially perivascular and visceral adipose tissue, becomes an active endocrine organ, producing a cascade of pro-inflammatory cytokines—interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1)—and pro-oxidative adipokines like leptin, resistin, and visfatin These mediators induce and maintain systemic inflammation, which activates endothelial dysfunction through the upregulation of adhesion molecules (e.g., VCAM-1, ICAM-1) and oxidative stress via the production of reactive oxygen species (ROS). This pro-inflammatory environment drives atherosclerosis, marked by plaque development, arterial stiffening, and decreased vascular compliance, which sets the stage for CVD.

In the cardiovascular system, such long-term exposure to these inflammatory and oxidative stressors leads to cardiomyocyte hypertrophy, interstitial fibrosis, and diastolic dysfunction, putting individuals at risk for heart failure with preserved or reduced ejection fraction. The kidneys also carry a similar burden, with proinflammatory cytokines and ROS leading to glomerular hyperfiltration, podocyte damage, and tubulointerstitial inflammation. This renal injury stimulates the renin-angiotensin-aldosterone system (RAAS), sodium retention, hypertension, and additional glomerular pressure, creating a vicious cycle of CKD progression. Insulin resistance, a central metabolic derangement, further worsens this cascade by inhibiting glucose uptake, increasing free fatty acids, and promoting lipid deposition in non-adipose tissues (e.g., liver, muscle), which increases oxidative damage and atherogenesis. The bidirectional interactions of

CKM are reflected in how CKD worsens metabolic control via uremic toxins (e.g., indoxyl sulfate), while hyperglycaemia drives vascular and renal deterioration via advanced glycation end-products (AGEs).

Genetic vulnerabilities, including polymorphisms in genes controlling fat distribution (e.g., FTO, PPARG), combine with environmental determinants such as calorie-rich diets and physical inactivity to influence disease severity. SDOH such as chronic psychosocial stress and restricted access to healthcare further amplify this pathophysiology by increasing cortisol levels and decreasing compliance with preventive interventions. The resulting chronic inflammation connects these organ systems in a self-perpetuating cycle that requires targeted interventions to break adipose-driven pathology and reduce multiorgan damage. It is important to understand this complex mechanism in order to formulate treatments which target the underlying causes instead of the symptoms of CKM syndrome.

CLINICAL FEATURES

The presentation of CKM syndrome changes with each stage, which mirrors the progressive engagement of metabolic, renal, and cardiovascular systems. At Stage 0, they show no gross signs, and act as the reference for primordial prevention with normal blood pressure, BMI, and glucose levels. At Stage 1, there are subclinical features revolving around adiposity, such as central obesity (waist >102 cm in men, >88 cm in women), increased BMI (more than 25 kg/m^2), and mild insulin resistance detectable by fasting glucose or HOMA-IR tests alone. Patients can be asymptomatic, although mild fatigue or decreased exercise capacity may become apparent. Stage 2 is the development of definite risk factors, and clinical manifestations include hypertension (systolic blood pressure >130 mmHg), dyslipidaemia (triglycerides >150 mg/dL, HDL <40 mg/dL in men, <50 mg/dL in women), and hyperglycaemia (fasting glucose 100-125 mg/dL). Mild CKD presentation is microalbuminuria (urine albumin-to-creatinine ratio 30-300 mg/g) or eGFR 60-89 mL/min/1.73 m^2, possibly with nocturia, mild edema, or frothy urine. Patients may present with nonspecific symptoms such as fatigue or polydipsia. Stage 3 involves subclinical CVD, as seen on imaging with coronary artery calcification, increased NT-proBNP (>125 pg/mL) reflecting beginning heart strain, or increasing proteinuria (>300 mg/g), usually without obvious symptoms but identifiable through screening. Mild exertional dyspnoea or swelling in the legs can occur. Stage 4 involves evident disease: CVD manifestations are angina, resting dyspnoea, palpitations, or neurological deficits post-stroke; CKD symptoms include anaemia (pallor and tiredness), bone pain (secondary hyperparathyroidism), or uremic features (nausea and pruritus); and T2D manifestations involve neuropathy (numbness, tingling), retinopathy (blurred vision), or diabetic foot ulcers. Risk accelerators exaggerate these characteristics: chronic inflammation appears as psoriasis exacerbations, rheumatoid arthritis joint stiffness, or fatigue with HIV; family history could be associated with premature disease; psychiatric illnesses such as depression decrease compliance with treatment; sleep disorders (obstructive sleep apnea) induce daytime sleepiness and hypoxemia; high high-sensitivity C-reactive protein (>2 mg/L) indicates systemic inflammation; and sex-specific factors are early menopause (hot flashes, osteoporosis risk) or polycystic ovary syndrome (acne, hirsutism, irregular menses). SDOH adds through barriers such as food deserts resulting in bad diet or absence of insurance postponing care, with ethnic differences (e.g., greater ectopic fat in South Asians at lower BMI) dictating presentation. These varied features require an integrative diagnostic framework to inform interventions.

TREATMENT

Management of CKM syndrome takes a holistic, stage-targeted approach to forestall cardiovascular

occurrences, treat risk factors, and treat established disease. During Stages 0-1, attention is given to primordial and primary prevention through life-style changes. This involves following a heart-healthy diet (e.g., Mediterranean diet high in fruits, vegetables, and omega-3 fatty acids), at least 150 minutes a week of moderate aerobic physical activity (e.g., brisk walking), and weight control to decrease adiposity. Behavioural management, including stress reduction and smoking stoppage, also is supportive of this stage. Stage 2 progresses to pharmacotherapy in addition to lifestyle modification, and the focus is on metabolic parameters. Antihypertensives (e.g., ACE inhibitors, ARBs) regulate BP, statins correct dyslipidaemia, and metformin or newer drugs such as SGLT2 inhibitors correct hyperglycaemia with added renal and cardiovascular protective effects. Elevation of eGFR and albuminuria is monitored regularly to manage CKD. Stage 3, with subclinical CVD, increases therapy to stabilize plaque and inhibit progression, including aspirin for risk of atherothrombosis and high-level lipid-lowering drugs (e.g., PCSK9 inhibitors) where necessary. Stage 4 follows proven guidelines: ADA guidelines for T2D (e.g., insulin if HbA1c >7%), ACC/AHA/HFSA guidelines for CVD and HF (e.g., beta-blockers, diuretics), and KDIGO guidelines for CKD (e.g., erythropoietin for anaemia). Multidisciplinary team management is key, including cardiologists, nephrologists, endocrinologists, nurses, pharmacists, dietitians, exercise therapists, mental health professionals, and social workers. Multidisciplinary team care models, as shown in trials such as COORDINATE-Diabetes, have raised evidence-based therapy prescription rates (e.g., SGLT2 inhibitors, GLP-1 receptor agonists) among heterogeneous populations, regardless of sex, race, or ethnicity. Patient support systems—family, religious organizations, or community groups—support adherence by offering emotional and practical support. Initiatives in health literacy, especially for socio-disadvantaged populations with increased metabolic risk, are essential to facilitate self-management.

NEWER ADVANCES

Advances in CKM syndrome in recent years, changing from 2024 and going on into 2025, are moving towards integrated and preventive measures.

A prominent 2025 AHA recommendation stresses lifestyle therapies for Stage 1, with individualized dietary regimens (e.g., DASH diet alterations), organized exercise regimens (e.g., resistance training), and behavioral therapy to treat adiposity and preclude worsening. Science has promoted a value-based care model, allowing for smooth transitions to augmented Stage 2 programs incorporating metabolic, renal, and cardiovascular risk management through personalized medicine strategies. Long-term studies correlate advanced CKM stages with higher mortality, emphasizing the need for early screening using measures such as the PREVENT equation, which includes SDOH and does not use race to ensure fair risk evaluation. Therapeutic innovations involve multi-action drugs, including SGLT2 inhibitors and GLP-1 agonists, that lower kidney failure, CV events, and weight at the same time, providing a three-prong approach.

Upcoming 2025 research identifies a new correlation between CKM and depression, leading to combined mental health screening and treatment (e.g., cognitive-behavioral therapy) to enhance adherence and outcome. In Asia, prevalence studies indicate a steep increase in CKM, necessitating region-specific prevention programs, such as community-based education campaigns. Development of metabolic syndrome is becoming more closely linked with CKM, including new research on CKD progression being associated with gut dysbiosis and inflammation, proposing probiotic treatments as a prospect. Later stages exhibit increased risks due to obesity and chronic inflammation, driving research for anti-inflammatory drugs (e.g., IL-6 inhibitors) and obesity drugs (e.g., semaglutide). Impediments

to evidence-based therapy adoption, including cost and awareness, are being addressed by policy changes and digital health platforms, improving access as of mid-September 2025. Collectively, these advances work towards overcoming disparities and enhancing long-term prognosis.

CONCLUSION

CKM syndrome presents as an important health construct bringing CVD, CKD, and metabolic disorders together into a staged, actionable paradigm. Its definition and classification yield a map from risk prevention to high care, and epidemiology points toward its worldwide reach and socioeconomic inequalities. Pathophysiology, fueled by adipose-induced inflammation, interconnects organ systems in a vicious cycle that requires targeted interruption. Clinical presentation progresses from insidious adiposity to multiorgan failure, mediated by varied risk enhancers and SDOH. Treatment utilizes lifestyle and drug therapy through multidisciplinary groups, while recent advancements are aimed at prevention, targeted therapies, and equality.

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Chapter 37

Weight Reduction and Remission of Type 2 Diabetes

Nilakshi Deka

INTRODUCTION

Traditionally, type 2 diabetes mellitus (T2DM) has been considered a chronic, progressive disease characterized by declining β-cell function and increasing dependence on pharmacotherapy. In recent years, research has challenged this paradigm. Remission T2DM means that a person with previously diagnosed diabetes maintains normal or near-normal blood glucose levels without the need for glucose-lowering medication for a sustained period of time. Clinical evidence suggests that remission of T2DM is achievable through substantial and sustained weight reduction, particularly in the early stages of disease. The recognition of remission has shifted the focus of management from chronic glycemic control to potentially curative interventions. Intensive lifestyle interventions, bariatric/metabolic surgery, and novel pharmacotherapies have demonstrated remarkable efficacy in inducing remission, with outcomes influenced by the degree and sustainability of weight loss, disease duration, and baseline β-cell function. This paradigm shift raises critical questions about the role of obesity and weight loss in the pathophysiology of diabetes and the sustainability of remission in clinical practice.

DEFINING REMISSION IN TYPE 2 DIABETES

Consensus definitions are essential for clinical trials and patient care. The ADA and international consensus groups define remission as HbA1c <6.5% (48 mmol/mol) maintained for at least three months in the absence of glucose-lowering medications. Remission can be classified as:

- **Partial remission**: HbA1c <6.5% or fasting glucose 100–125 mg/dL (5.6–6.9 mmol/L) without pharmacotherapy for ≥1 year.
- **Complete remission**: Normal glucose levels (HbA1c <5.7%) without pharmacotherapy for ≥1 year.
- **Prolonged remission**: Complete remission maintained for ≥5 years

These definitions distinguish remission from "cure," acknowledging the risk of relapse if weight is regained or metabolic stress re-emerges.

Latest guideline:

1. **Operational definition (current standard):**
    - **HbA1c < 6.5%** (or equivalent glycemic measure) **for at least 3 months without any glucose-lowering pharmacologic therapy**. Measure the HbA1c no sooner than 3 months after stopping therapy. This is the definition established by the 2021 international consensus and reiterated in subsequent reviews and guidelines.
2. **When HbA1c is unreliable:**
    - Use **fasting plasma glucose < 126 mg/dL (7.0 mmol/L)** or CGM-

derived metrics (GMI) as alternatives, with the same requirement of ≥3 months off therapy before declaring remission.

3. **Terminology / Rationale:**
    - The consensus prefers the term **"remission"** (not "cure"), because metabolic dysfunction may persist and relapse can occur; thus ongoing monitoring is required.
4. **Timing and monitoring recommendations:**
    - Document baseline glycemia before therapy withdrawal.
    - Confirm remission by testing ≥3 months after stopping medications.
    - Continue **regular follow-up monitoring** for glycemia and diabetes complications (at least annually, more often as clinically indicated). Recent guideline documents (IDF 2025 and nutrition/remission reviews) emphasize continued surveillance and weight-maintenance support.
5. **Clinical context emphasized by recent guidelines (2023–2025):**
    - **Early intervention** (shorter diabetes duration) and **magnitude/ sustainability of weight loss** are repeatedly noted as the strongest determinants of achieving and maintaining remission.
6. **Real-world evidence & cautions:**
    - Large real-world analyses and recent cohort reports show remission is achievable but **uncommon** at population scale and that **relapse rates are substantial** (a notable fraction of those who remit will resume medication in subsequent years). Practitioners should set realistic expectations and plan long-term follow-up.

CLINICAL STEPS (CHECKLIST)

1. **Baseline**
    - Document HbA1c and current medications.
2. **Therapy withdrawal**
    - Stop glucose-lowering medications (if safe).
3. **Timing**
    - Wait at least **3 months** after withdrawal.
4. **Test glycemia**
    - HbA1c (preferred)
    - Alternatives: FPG, CGM (if HbA1c unreliable).
5. **Confirm remission**
    - HbA1c < 6.5% (or equivalent) at ≥3 months off meds.
6. **Monitoring**
    - Continue **annual HbA1c/FPG testing**.
    - Screen for diabetes complications (retinopathy, nephropathy, neuropathy, CVD).
7. **Support**
    - Reinforce **weight maintenance, lifestyle changes**.
    - Consider pharmacotherapy/surgery for sustained weight loss if needed.

MECHANISMS BY WHICH WEIGHT REDUCTION INDUCES REMISSION

- **Reduction in hepatic fat and improved insulin sensitivity:** Caloric restriction rapidly reduces intrahepatic fat, normalizing

hepatic insulin sensitivity within 7 days and reducing fasting plasma glucose.

- **Reduction in pancreatic fat and restoration of β-cell function:** Sustained weight loss reduces pancreatic triglyceride accumulation, improving β-cell insulin secretion, especially in individuals with shorter disease duration.
- **Improvement in peripheral insulin sensitivity:** Weight reduction enhances skeletal muscle glucose uptake, reversing peripheral insulin resistance.
- **Alteration in adipokines and inflammatory mediators:** Obesity promotes chronic low-grade inflammation through cytokines such as TNF-α and IL-6. Weight loss reduces systemic inflammation and improves insulin sensitivity.
- **Gut hormone changes:** Bariatric surgery and GLP-1 receptor agonists alter gut hormone responses, enhancing satiety and insulin secretion, further supporting remission.

CLINICAL EVIDENCE FOR REMISSION THROUGH WEIGHT REDUCTION

Lifestyle interventions

The **Diabetes Remission Clinical Trial (DiRECT)** demonstrated that intensive low-calorie diets achieved remission in 46% of patients at one year, with durability in 36% at two years. Weight loss magnitude was the strongest predictor, with 86% remission in individuals losing ≥15 kg. Similarly, the Look AHEAD trial reported partial remission in 11.5% of participants at one year and 7.3% at four years following intensive lifestyle interventions.

Bariatric/metabolic surgery

Bariatric surgery is the most effective intervention for sustained weight loss and diabetes remission.

- **Roux-en-Y gastric bypass (RYGB)** and **sleeve gastrectomy** induce remission in 60–80% of patients within 1–2 years.
- Long-term follow-up indicates sustained remission in 25–50% of patients at 10 years, depending on weight maintenance.
- Surgery induces hormonal changes (GLP-1, PYY, ghrelin) that contribute to glycemic improvement beyond weight loss.

Pharmacotherapy

Recent advances in pharmacological therapy bridge the gap between lifestyle interventions and surgery:

- **GLP-1 receptor agonists (semaglutide)**: Achieve ~15% body weight reduction and substantial HbA1c improvement, with many participants achieving remission.
- **Dual GIP/GLP-1 agonists (tirzepatide)**: Demonstrated up to 20% weight loss in trials, with normalization of glucose metabolism in many participants.

PREDICTORS OF REMISSION

Not all individuals with T2DM achieve remission following weight loss. Predictors include:

- **Duration of diabetes**: Shorter duration (<6 years) is strongly associated with remission.
- **Extent of weight loss**: ≥15 kg weight loss strongly predicts remission.
- **Residual β-cell function**: Preserved C-peptide levels indicate greater capacity for recovery.
- **Absence of insulin therapy**: Patients not requiring insulin are more likely to achieve remission.

SUSTAINABILITY AND RELAPSE

Remission is not always permanent. Weight regain often leads to relapse, highlighting the importance of long-term weight management. The DiRECT trial showed that 70% of those who maintained >10 kg weight loss at two years remained in remission. Even

if remission is not sustained, periods of normoglycemia reduce complication risks ("legacy effect").

CONCLUSION

Weight reduction represents the most powerful modifiable factor for achieving remission of type 2 diabetes. Evidence from lifestyle interventions, bariatric surgery, and pharmacotherapy demonstrates that remission is achievable, especially in early disease stages and with substantial, sustained weight loss. While challenges remain in ensuring long-term sustainability and accessibility, the concept of remission offers a transformative paradigm shift in diabetes management.

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Chapter 38

Injectable GLP-1 Receptor Agonists: Treatment Considerations in Diabetes vs Obesity

Arundhati Dasgupta

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed the management of type 2 diabetes (T2D) and, more recently, obesity. Although initially developed for glycemic control, their pleiotropic benefits including weight reduction, cardiovascular protection, and metabolic improvements have positioned them at the intersection of endocrinology and obesity medicine. This review provides a comparative analysis of the clinical, pharmacological and therapeutic considerations of injectable GLP-1 RAs in diabetes and obesity.

GLP-1 RAs mimic the incretin hormone thereby enhancing glucose dependent insulin secretion, suppressing glucagon, slowing gastric emptying. GLP-1 RAs also decrease pancreatic β-cell apoptosis and promote their proliferation. Other functions of GLP-1 include increased glucose uptake in the muscles, decreased glucose production in the liver, neuroprotection, and reduction in appetite with increased satiety due to direct actions on the hypothalamus. These mechanisms underlie their dual indication in diabetes and obesity, but the relative importance of pathways differs, with glycemic modulation predominating in diabetes, while appetite regulation and caloric restriction dominate in obesity management. In terms of cardiovascular effects, GLP-1 agonists have been shown to improve left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function while reducing infarction size and overall risks for a cardiovascular event.

Initially introduced as daily injections (e.g., exenatide, liraglutide), the class has now expanded to longer-acting weekly agents (e.g., semaglutide) delivering more potent glycemic and weight-loss effects. In T2D, GLP-1 RAs are now core antihyperglycemic agents with proven or suggested cardiovascular (CV) benefit in high-risk patients; in obesity medicine, higher-dose formulations provide clinically meaningful and sustained weight loss. The clinical decision to use a GLP-1 RA depends on whether the primary indication is glycemic control or weight reduction which affects drug and dose choice, expected benefits, monitoring, and counselling.

PHARMACOKINETICS AND DOSING

GLP-1 RAs vary by molecular structure (exendin-4 analogues vs human GLP-1 analogues), half-life, dosing frequency, and central versus peripheral effects. Short-acting agents exert more pronounced postprandial glucose effects (via delayed gastric emptying); long-acting agents provide greater fasting glucose and HbA1c reduction and typically larger sustained weight loss.

Importantly, regulatory approvals often differ by dose: the same active molecule has been approved at different doses and for different indications (for example, semaglutide 0.5–1.0 mg weekly for T2D vs semaglutide 2.4 mg weekly for obesity; liraglutide

1.8 mg for T2D vs 3.0 mg for weight management). Dose selection therefore must reflect the clinical objective (glycemic control vs maximal weight loss) and regulatory labeling.

DOSING AND PHARMACODYNAMIC NUANCES

GLP-1RAs exert their effects in a dose-dependent manner, but the pharmacodynamic emphasis differs: pancreatic β-cell stimulation and glucagon suppression predominate at lower doses used in diabetes, while central appetite suppression and delayed gastric emptying dominate at higher doses prescribed for obesity. Consequently, dose-response curves for glycemic and weight diverge beyond the glycemic plateau explaining why semaglutide 1 mg plateaus for glucose control but semaglutide 2.4 mg continues to drive further weight reduction.

Agent	Frequency	Half-life	Typical Dose in Diabetes	Typical Dose in Obesity
Exenatide	Twice daily	2.4 h	5–10 µg BID	Not approved
Liraglutide	Daily	13 h	1.2–1.8 mg	3.0 mg
Dulaglutide	Weekly	90 h	0.75–1.5 mg	Up to 4.5 mg explored
Semaglutide	Weekly	168 h	0.5–1.0 mg	2.4 mg
Tirzepatide*	Weekly	120 h	5–15 mg	10–15 mg

(*Tirzepatide is a dual GLP-1/GIP receptor agonist but included for clinical relevance.).

Table 1. Comparative pharmacokinetics of GLP1RAs in patients with diabetes vs patients with obesity

CLINICAL EFFICACY

1.GLYCEMIC OUTCOMES (IN DIABETES)

Across pivotal head-to-head trials, injectable GLP-1RAs demonstrate robust glycemic efficacy, with mean HbA1c reductions ranging from ~1.0% to 1.8% depending on baseline HbA1c and agent used. The *SUSTAIN-7* trial comparing semaglutide (0.5 mg and 1.0 mg once weekly) with dulaglutide (0.75 mg and 1.5 mg once weekly) found semaglutide achieving greater HbA1c reductions (−1.6% vs −1.3% at higher doses; $p<0.001$), alongside superior weight reduction. Similar findings were observed in *SURPASS-2*, where tirzepatide, a dual GIP/GLP-1 RA, outperformed semaglutide 1 mg with HbA1c reductions of up to −2.3%, underscoring its enhanced incretin potency.

Moreover, GLP-1RAs exhibit distinct durability of glycemic control, as evidenced by extension data from *SUSTAIN FORTE* and *AWARD-11*, where HbA1c lowering was maintained over 52–104 weeks with minimal attenuation. The longer-acting weekly formulations (semaglutide, dulaglutide) and dual agonists (tirzepatide) provide smoother glycemic profiles with less glycemic variability and minimal hypoglycemia risk compared to shorter-acting agents

like exenatide BID.

However, in individuals with obesity but without diabetes, baseline HbA1c and endogenous insulin response substantially influence glycemic outcomes. Trials such as *STEP 1* (semaglutide 2.4 mg) and *SURMOUNT-1* (tirzepatide 5–15 mg) demonstrated modest yet clinically relevant reductions in fasting glucose and HbA1c (typically −0.3% to −0.4%), reflecting improved insulin sensitivity and β-cell responsiveness. Thus, while glycemic improvements are secondary in obesity trials, they signify metabolic restoration accompanying adiposity reduction.

Another key consideration lies in the ceiling effect of glycemic benefit. In T2DM patients with high baseline HbA1c (>9%), the absolute reduction achieved with semaglutide or tirzepatide may exceed 2%, whereas in patients with near-target HbA1c or non-diabetic obesity, the glycemic impact is blunted but accompanied by greater weight loss proportionally.

2. WEIGHT LOSS OUTCOMES (IN OBESITY)

The degree of weight loss varies considerably depending on baseline BMI, presence or absence of diabetes, and the specific GLP-1RA molecule used. Long-acting GLP-1RAs (e.g., semaglutide, dulaglutide, tirzepatide) achieve greater weight reductions than short-acting agents (e.g., exenatide BID, lixisenatide), as sustained receptor engagement more effectively suppresses appetite and delays gastric emptying. The dual incretin agonist tirzepatide, through concurrent GIP and GLP-1 receptor activation, amplifies adipose tissue lipolysis and thermogenesis, explaining the superior weight-loss efficacy observed in head-to-head comparisons. The *SURPASS-2* and *SURMOUNT-1* results firmly establish tirzepatide's position as the most potent incretin-based anti-obesity therapy to date.

In general, individuals without diabetes tend to achieve greater proportional weight loss than those with type 2 diabetes.In semaglutide trials, this divergence was most striking. The *STEP 1* study, evaluating semaglutide 2.4 mg weekly in adults with obesity without diabetes, demonstrated a mean weight reduction of −14.9% over 68 weeks, compared to −2.4% with placebo (p<0.001). In contrast, *SUSTAIN 7* and *SUSTAIN FORTE*, conducted in T2DM populations, reported smaller though still significant mean losses (−6–7% range), underscoring the differential physiological milieu between euglycemia and diabetes. Similarly, the *SURMOUNT-1* trial with tirzepatide (5–15 mg) in non-diabetic obesity participants showed mean weight reductions of −15% to −21%, exceeding those seen in *SURPASS-2* (−8–12%) among diabetic participants.

Mechanistically, these differences arise from distinct central and peripheral pathways. In obesity, GLP-1RAs exert potent central satiety effects via activation of GLP-1 receptors in the hypothalamic arcuate nucleus, decreasing appetite and energy intake. In diabetes, however, partial leptin resistance, insulin therapy, and glycemic instability attenuate these central effects.Preserved β-cell function and reduced adaptive metabolic resistance also could be factors responsible for better results among non diabetic obese .

In clinical translation, weight reduction of ≥10% achievable with semaglutide 2.4 mg or tirzepatide 10–15 mg correlates with meaningful metabolic improvements, including reversal of prediabetes and enhanced insulin sensitivity,

3. CARDIOVASCULAR OUTCOMES

Key studies showing evidence of cardiovascular benefit for GLP-1RAs in the diabetes-focused cardiovascular outcome trials (CVOTs) include

- **LEADER (liraglutide):** 13% relative risk reduction (RRR) in major adverse cardiovascular events (MACE) in T2DM patients with established CV disease
- **SUSTAIN-6 (semaglutide)**: 26% RRR in MACE.

- **REWIND (dulaglutide):** Significant MACE reduction even in a majority population without prior CVD.
- **HARMONY and EXSCEL**: Albiglutide and exenatide showed CV safety with modest benefit.

These findings firmly established GLP-1RAs as CV risk-reducing agents in diabetes.

However, the SELECT trial revolutionised this understanding by demonstrating CV protection in non-diabetic obese individuals. This double-blind, placebo-controlled, randomised trial involving 17,604 adults with BMI ≥27 kg/m² with established cardiovascular disease, and no diabetes showed a 20% RRR in MACE(HR 0.80; 95% CI 0.72–0.90; p<0.001) and a 15% CV death reduction (HR 0.85; 95% CI 0.71–1.01) in the semaglutide 2.4 mg weekly arm vs the placebo arm.This pivotal evidence has shifted global guidelines with both ADA 2025 and EASD 2024 now acknowledging GLP-1RAs as first-line pharmacotherapy for obesity in patients with cardiometabolic risk, even without diabetes.

SAFETY AND TOLERABILITY

Gastrointestinal side effects (nausea, vomiting, diarrhea) remain the most common and are dose-dependent. In obesity, lean-mass preservation and gallbladder monitoring gain importance as patients experience larger absolute fat losses. Gradual titration mitigates intolerance.

COMPARATIVE CONSIDERATIONS

Although the same class of injectable GLP-1 receptor agonists underpins the management of both type 2 diabetes mellitus and obesity, the therapeutic rationale, pharmacologic targets, clinical expectations and time to effect differ markedly between the two indications. Titration schedules are slower in obesity therapy to minimise gastrointestinal intolerance, as treatment duration is long-term and adherence is crucial.

PATIENT-CENTRIC AND SYSTEMIC PERSPECTIVES

High acquisition costs, variable insurance coverage (diabetes vs obesity indication), and supply

Parameter	Diabetes CVOTs	SELECT (Obesity)
Population	T2DM with/without CVD	Non-diabetic, CVD + obesity
Agent	Liraglutide, Dulaglutide, Semaglutide (≤1 mg)	Semaglutide 2.4 mg
MACE reduction	13–26%	20%.
Mechanistic driver	Glycemia + weight + direct vascular effect	Weight + anti-inflammatory + endothelial
Implication	CV protection in diabetes	CV protection in obesity

Table 2. Comparision of cardiovascular benefits with GLP1RAs in patients with diabetes vs patients with obesity

Aspect	Diabetes	Obesity
Primary endpoint	HbA1c reduction, glycemic stability	% body weight reduction
Secondary	Weight loss, CV/renal protection	Metabolic improvement, CV risk
Time to effect	2–4 weeks for glucose	8–12 weeks for visible weight change
Target dose	Lower	Higher
Titration speed	Faster	Slower (for tolerability)

Table 3. Comparative therapeutic considerations of GLP1RAs in patients with diabetes vs patients with obesity

constraints are major practical barriers in the use of GLP1RAS. From a health-system viewpoint, access and reimbursement remain more favorable in diabetes than in obesity. This creates ethical and logistical dilemmas: two patients with similar cardiometabolic risk might receive different treatment access based purely on diagnostic coding. However, policy revisions are gradually changing to address this imbalance.

CONCLUSION

Diabetes and obesity, long viewed as distinct metabolic entities are now seen as points on the same continuum of insulin resistance, inflammation, and cardiovascular risk. GLP-1RAs, exemplified by semaglutide and tirzepatide, have emerged as the first pharmacologic bridge between these conditions. The differentiation now lies not in the mechanism but in clinical intent and dosing precision, heralding a unified paradigm of "metabolic disease management" rather than separate pillars of diabetes and obesity therapy.

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Chapter 39

Dual GLP-1 and GIP Receptor Agonists: A Paradigm Shift in Diabesity Management

Kunjan Saikia

INTRODUCTION

The concept of "diabesity" underscores the complex interplay between these two conditions, where managing one often impacts the other. As practitioners, we are well aware of the intricate relationship between type 2 diabetes and obesity. Recent advances in pharmacotherapy have led to the development of dual GLP-1 and GIP receptor agonists, offering a promising therapeutic approach for diabesity management.

PHYSIOLOGY OF GLP-1 AND GIP

GLP-1 (Glucagon-Like Peptide-1) and GIP (Glucose-Dependent Insulinotropic Polypeptide) are incretin hormones that play a crucial role in glucose metabolism. GLP-1 enhances glucose-dependent insulin secretion, slows gastric emptying, and reduces glucagon production. GIP also stimulates insulin secretion and improves glucose metabolism. The dual action of these hormones provides a rationale for targeting both receptors in diabesity management.

MECHANISM OF ACTION

The mechanism of action of dual GLP-1 and GIP receptor agonists involves the activation of both GLP-1 and GIP receptors, leading to:
1. Enhanced glucose-dependent insulin secretion: Dual agonists enhance glucose-dependent insulin secretion, improving glycemic control.
2. Slowed gastric emptying: Dual agonists slow gastric emptying, reducing the rate at which glucose enters the bloodstream.

3. Reduced glucagon production: Dual agonists reduce glucagon production, which helps lower blood glucose levels.

DUAL GLP-1 AND GIP RECEPTOR AGONISTS: A NOVEL APPROACH

Dual GLP-1 and GIP receptor agonists, such as **tirzepatide**, have shown significant promise in clinical trials. By targeting both GLP-1 and GIP receptors, these medications offer a comprehensive approach to managing diabesity. The benefits of dual agonists include:

1. Improved glycemic control: Dual agonists have been shown to improve glycemic control in patients with type 2 diabetes, reducing HbA1c levels and improving glucose metabolism.

2. Weight loss: These medications can also promote significant weight loss, which is beneficial for patients with obesity and type 2 diabetes.
3. Cardiovascular benefits: Some studies suggest that dual GLP-1 and GIP receptor agonists may have cardiovascular benefits, such as reducing blood pressure and improving lipid profiles.

CLINICAL TRIALS AND EVIDENCE

The typical dose of **tirzepatide** for diabetes is 5–15 mg once a week and for obesity is 10–15 mg once a week.

Tirzepatide, acts via concurrent GIP and GLP-1 receptor activation, amplifies adipose tissue lipolysis and thermogenesis, with superior weight-loss efficacy observed in head-to-head comparisons. The SURPASS and SURMOUNT results decisively establish tirzepatide's position as the utmost effective incretin-based anti-obesity therapy to date and also its effectiveness in type 2 diabetes.

Several other clinical trials have demonstrated the efficacy and safety of dual GLP-1 and GIP receptor agonists in treating diabesity. These trials have shown that these medications can:

1. Improve glycemic control: Dual agonists have been shown to improve glycemic control in patients with type 2 diabetes, reducing HbA1c levels and improving glucose metabolism.

2. Promote weight loss: These medications with gradual increment of doses can also promote significant weight loss, which is beneficial for patients with obesity and type 2 diabetes. 3. Reduce cardiovascular risk: Some studies suggest that dual GLP-1 and GIP receptor agonists may have cardiovascular benefits, such as reducing blood pressure and improving lipid profiles.

POTENTIAL SIDE EFFECTS AND LIMITATIONS

While dual GLP-1 and GIP receptor agonists have shown promise in treating diabesity, they may also have potential side effects and limitations. These include:

1. Gastrointestinal side effects: Dual agonists may cause gastrointestinal side effects, such as nausea, vomiting, and diarrhea.

2. Increased risk of pancreatitis: There may be an increased risk of pancreatitis associated with the use of dual GLP-1 and GIP receptor agonists. 3. Cost and accessibility: These medications may be expensive, and accessibility may be limited in some regions.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

As endocrinologists, we must consider the clinical implications of dual GLP-1 and GIP receptor agonists in diabesity management. These medications offer a valuable addition to our therapeutic armamentarium, particularly for patients who require comprehensive management of both diabetes and obesity. Future studies should focus on long-term efficacy, safety, and cardiovascular outcomes.

CONCLUSION

Dual GLP-1 and GIP receptor agonists represent a significant advancement in the treatment of diabesity. Their ability to improve glycemic control, promote weight loss, and potentially offer cardiovascular benefits makes them an attractive therapeutic option for patients with type 2 diabetes and obesity. As endocrinologists, we must stay abreast of the latest developments in this field and consider the potential benefits of these medications in our patients. The future of dual GLP-1 and GIP receptor agonists in diabesity management looks promising. Ongoing research and clinical trials will continue to elucidate the benefits and limitations of these medications. As our understanding of the complex interplay between diabetes and obesity evolves, we can expect to see further innovations in the treatment of diabesity.

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Section 12

Section Editor : **Sanjib Medhi**

Diabetes and Morbidities of Clinical Importance

Chapter 40

MASLD in Diabetes: How to Manage?

Soumik Goswami
Rajat Deb

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly NAFLD, is common but often unrecognized in people with type 2 diabetes. It may progress from steatosis to steatohepatitis (MASH), cirrhosis, or even liver cancer and is associated with cardiovascular disease, extrahepatic cancers, and worsened quality of life. Despite this, many remain unaware of MASLD's serious hepatic and extrahepatic risks, and the need for early detection. This chapter covers its epidemiology, pathophysiology, risk stratification, and management.

EPIDEMIOLOGY

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM), and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) are two rapidly escalating concerns across global health systems. MASLD is now the most common cause of chronic liver disease globally, and its prevalence continues to rise. A meta-analysis by Younossi et al, which reviewed 80 studies from 20 countries and included 49,419 participants, found that 55.5% of people with T2D have steatosis, twice the prevalence seen in the general population. Among South Asian patients with T2D, the rate was even higher at 57.87%. The study also showed that 37.3% of type 2 diabetic patients globally have steatohepatitis (MASH), and 17% have advanced liver fibrosis. A study from eastern India among patients with T2D reported the prevalence of steatosis as 59% with fibrosis present in nearly one-fourth of the study participants. These trends point to a significant burden of liver disease in people with diabetes worldwide.

PATHOPHYSIOLOGY

The association between type 2 diabetes mellitus (T2DM) and MASLD is bidirectional and multifaceted. MASLD encompasses a spectrum of hepatic disorders that may progress from simple steatosis to MASH, cirrhosis, and hepatocellular carcinoma. Although the underlying mechanisms are not yet fully elucidated, lifestyle factors along with individual genetic susceptibility are believed to play a pivotal role in disease initiation and progression. Multiple pathophysiological pathways linking MASLD and T2DM have been proposed, several of which are now well established. Insulin resistance lies at the core of this interaction, affecting the liver, muscle, and adipose tissue even in lean individuals with MASLD, thereby predisposing them to hyperglycemia and subsequent diabetes. In parallel, impaired beta-cell function prevents adequate compensation for peripheral insulin resistance, further facilitating disease progression. Glucotoxicity adds another layer of metabolic stress, perpetuating insulin resistance and accelerating the transition from simple steatosis to steatohepatitis. De novo lipogenesis, driven largely by excess carbohydrate and fructose intake, not only

contributes to hepatic steatosis but also generates lipotoxic metabolites that damage hepatocytes, pancreatic beta cells, and other peripheral tissues. Taken together, the convergence of these mechanisms highlights the intertwined natural history of MASLD and diabetes, emphasizing the need for integrated management strategies targeting both metabolic and hepatic outcomes.

DIAGNOSIS AND RISK STRATIFICATION

In MASLD, histological staging of fibrosis emphasizes two critical points: clinically significant fibrosis (≥F2), which is linked to higher cardiovascular risk, mortality, and remains reversible with treatment; and cirrhosis, which carries the highest risk, especially in patients with obesity and type 2 diabetes, and mandates surveillance for oesophageal varices, hepatic decompensation, and hepatocellular carcinoma. Liver biopsy, once the gold standard for assessing fibrosis, is limited by invasiveness, patient discomfort, risk of complications, and sampling variability. Non-invasive tests (NITs) are now preferred for risk stratification and follow-up in MASLD. Blood-based scores, particularly the Fibrosis-4 Index (FIB-4), calculated using age, ALT, AST, and platelet count, is inexpensive, validated by long-term outcomes, and recommended as first-line screening tools to exclude advanced fibrosis. Imaging techniques, including vibration-controlled transient elastography (VCTE), shear wave elastography (SWE), and magnetic resonance elastography (MRE), provide reliable assessment of liver stiffness. Among these, transient elastography (FibroScan®) is widely used, with liver stiffness measurements (LSM) serving as a surrogate marker of fibrosis severity and has shown high diagnostic performance for fibrosis assessment. Wong et al. reported that an LSM cut off >7.9 kPa identified significant fibrosis (≥F2) with 91% sensitivity, 97% negative predictive value (NPV), 75% specificity, and 52% positive predictive value (PPV), unaffected by inflammation, steatosis, or BMI. Similarly, Siddiqui et al. demonstrated that an LSM <12 kPa reliably excluded cirrhosis with a 99% NPV, supporting TE as an effective tool to distinguish early from advanced fibrosis. As per the guidelines, physicians and first-contact healthcare workers should screen for liver steatosis and fibrosis among high-risk patients like those having diabetes mellitus and obesity. Given this recommendation, many algorithms have been proposed by international bodies for sequential assessment of liver fibrosis using NITs **(Fig 1)**. FIB-4 remains a widely validated tool for initial screening, particularly due to its simplicity and cost-effectiveness. Studies have demonstrated its utility in distinguishing between low-risk and high-risk patients, although cut-off values for optimal performance vary across populations. In a study conducted on Indian T2D patients with MASLD, the optimal FIB-4 cut off for identifying MASLD patients at risk of fibrosis, using Transient Elastography (TE) as the gold standard, was found to be 1.5 (instead of 1.3), with a sensitivity of 83%, specificity of 80%, negative predictive value of 94% and diagnostic accuracy of 81%. While current guidelines suggest a FIB-4 cut-off of <1.3 for ruling out significant liver fibrosis, this threshold may need adjustment based on demographic and geographical variations.

MANAGEMENT

Lifestyle Modification and Weight Loss

Lifestyle modification, including dietary changes and increased physical activity, is the cornerstone of managing MASLD. Clinical guidelines and multiple studies consistently recommend a weight loss of 7–10% of initial body weight to achieve significant improvements: this degree of weight loss is associated with resolution of steatosis, improvement or resolution of steatohepatitis, and regression of fibrosis in a substantial proportion of patients. Specifically, weight loss of ≥5% improves liver steatosis, while ≥7–10% is required for histological

resolution of steatohepatitis and fibrosis regression. For example, one prospective study found that 58% of patients who lost ≥5% of their weight achieved NASH resolution, and 90% of those losing ≥10% had NASH resolution, with 45% showing fibrosis regression.

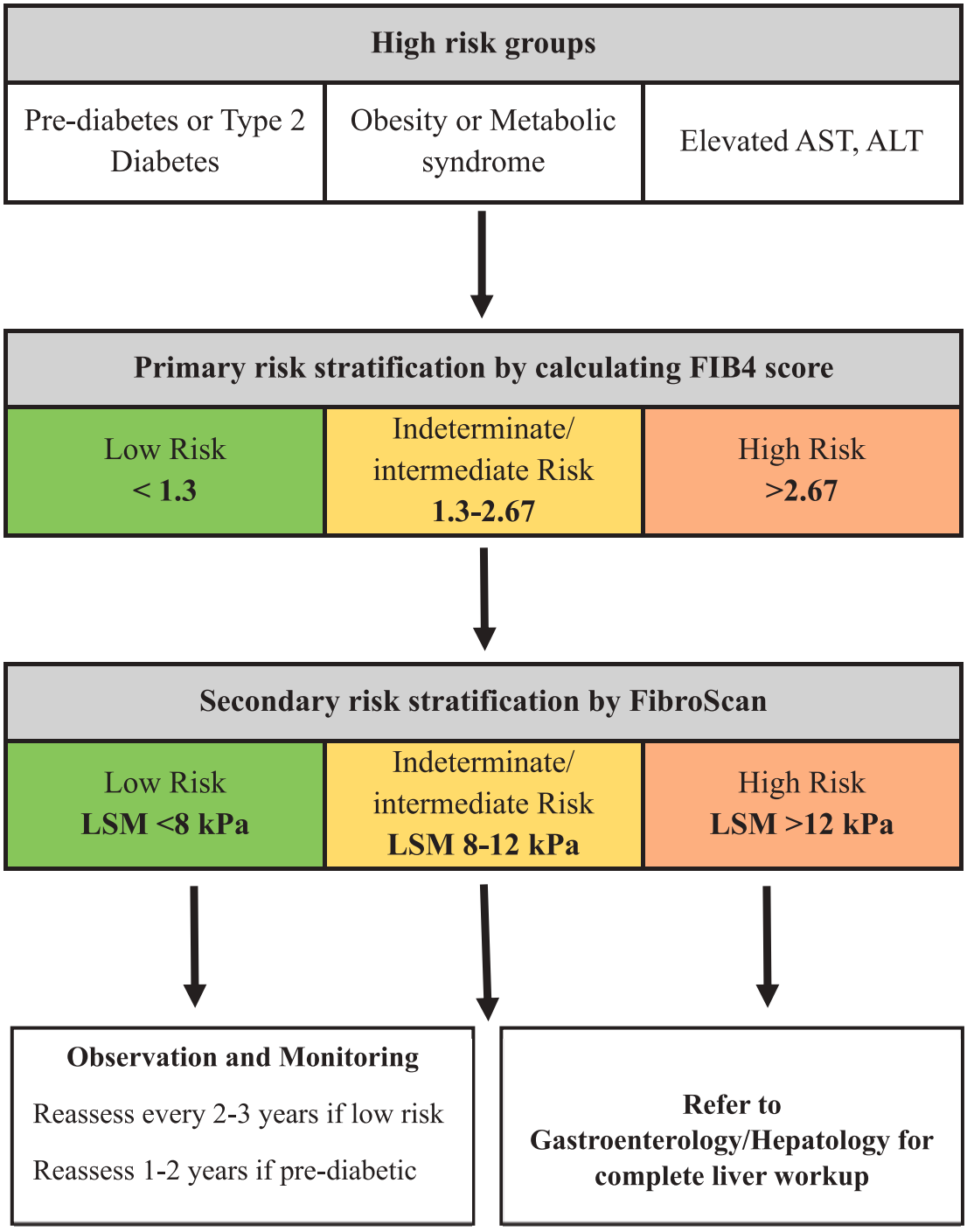

Fig 1: Risk stratification for liver fibrosis related to diabetes

Table 1: Weight loss thresholds and their impact on liver disease resolution.

Weight Loss (%)	Steatosis Improvement	Steatohepatitis Resolution	Fibrosis Regression
≥5%	Yes	Some	Rare
7–10%	Yes	Yes	Yes
≥10%	Yes	Up to 90%	Up to 45%

Pharmacological Management of MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly managed with pharmacological agents targeting metabolic, inflammatory, and fibrotic pathways. Four promising drug classes— PPAR α/γ agonist, GLP-1Ra, THR-β agonist, and SGLT2 inhibitors—are at the forefront of MASLD therapy.

Saroglitazar

Saroglitazar, a dual PPAR α/γ agonist, has shown efficacy in improving glycemic control, lipid profile, liver enzymes, and non-invasive markers of steatosis, steatohepatitis and fibrosis in MASLD patients with type 2 diabetes. In a prospective case series, saroglitazar 4 mg daily led to significant reductions in HbA1c, triglycerides, ALT, and transient elastography parameters (CAP and LSM) over 32 weeks, suggesting benefits for both metabolic and hepatic outcomes. Although approved for MASLD management in India, larger randomized controlled trials are needed to demonstrate efficacy in fibrosis reduction and to establish long-term safety.

Semaglutide

Semaglutide, a GLP-1 receptor agonist, is primarily used for management of diabetes and obesity but has also shown benefit in MASLD. The Phase III ESSENCE study has demonstrated resolution of steatohepatitis in 63% and reduction of liver fibrosis in 37% of patients with biopsy-defined MASH and fibrosis stage 2 or 3. Semaglutide's benefit is attributed to weight loss, improved insulin sensitivity, and possibly a direct hepatic effect and it has received an accelerated USFDA approval for MASLD management.

Resmetirom

Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, is the first USFDA-approved drug for management of MASLD with moderate to advanced fibrosis. Meta-analyses and a phase 3 trial show significant reduction in liver fat (MRI-PDFF), improvement in liver enzymes, lowering of LDL cholesterol and triglycerides along with histological improvement in steatohepatitis and fibrosis. Adverse events are generally mild, with gastrointestinal symptoms being the most common.

SGLT2 inhibitors

SGLT2 inhibitors, originally developed for hyperglycaemia management, have shown hepatoprotective effects in MASLD, especially in patients with type 2 diabetes. Clinical trials and real-world studies report significant reductions in liver fat (MRI-PDFF), aminotransferases, and fibrosis indices (FIB-4, APRI). SGLT2 inhibitors may also reduce the risk of esophageal varices and extrahepatic cancers. A biopsy-driven RCT in 154 adults with MASH, with or without type 2 diabetes,

showed that treatment with dapagliflozin resulted in significant MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH.

Other categories of anti-diabetic drugs, particularly pioglitazone (a PPAR γ agonist) and GLP-1 receptor agonists such as liraglutide and dulaglutide, have demonstrated beneficial effects in MASLD. Pioglitazone is associated with significant improvements in steatosis and steatohepatitis, but the data on fibrosis improvement is equivocal. GLP-1 receptor agonists, including liraglutide and dulaglutide, have shown reductions in liver fat, improvements in liver enzymes, and histological benefits, with some studies reporting resolution of steatohepatitis without worsening fibrosis. A phase 2 study with Tirzepatide (GLP-1Ra/GIP co-agonist) has shown resolution of steatohepatitis and possible reduction of fibrosis but further trials in MASLD have not been planned with this molecule. [41] Metformin, while widely used for diabetes, has not shown clear histological benefits for MASLD, though it may improve liver enzymes. DPP-4 inhibitors and sulfonylureas have limited effects on MASLD progression, and insulin therapy may reduce steatosis and improve liver enzymes, but its impact on fibrosis is not well established. A multifaceted approach, often combining these agents, is recommended for optimal MASLD management.

CONCLUSION

MASLD is highly prevalent in patients with type 2 diabetes and contributes significantly to both hepatic and extrahepatic morbidity. Early detection, primarily through non-invasive tests, is essential for risk stratification and timely intervention. Lifestyle modification remains the cornerstone of therapy, complemented by emerging pharmacological options with promising benefits. An integrated, multidisciplinary approach that addresses both metabolic and hepatic targets is therefore crucial to improve outcomes and reduce the long-term burden of MASLD in diabetes.

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Chapter 41

Rheumatic Disorders in Diabetes

Parvati Nandy

Rheumatic disorders include problems in joints, soft tissues, blood vessels and, other connective tissues, majority being autoimmune. This field is multi-disciplinary and there is ample overlap with other branches of Medicine, notably the endocrine system.

Soft tissue rheumatism refers to local diseases affecting the joint and structures around the joints including tendons, ligaments, capsules, nerves, muscles, nerve entrapments, vascular lesions and ganglia.

Prevalence of musculoskeletal disorders in patients with or without diabetes.

Prevalence of musculoskeletal disorders in patients	With diabetes	Without diabetes
Adhesive capsulitis (Frozen Shoulder)	11-30%	2-10%
Limited joint mobility	8-50%	0-26
Dupuytren's contracture	20-63%	13%
Carpal Tunnel syndrome	11-16%	125/100000
Flexor tenosynovitis	11%	<1%
Diffuse idiopathic skeletal hyperostosis	13-49%	1.6-13%

Diabetes mellitus **(DM)** is a serious and chronic multi systemic disorder of carbohydrate metabolism linked to insulin resistance, glucotoxicity, and collagen cross linking. Hyperglycemia also leads to blood vessel microangiopathy and formation of advanced glycation end products. This forms the basis of the rheumatic disorders of diabetes. Glycation of ligaments is increased in Diabetes, they become thickened and stiff, limiting flexibility of joints and promoting joint contractures. This forms the basis of soft tissue rheumatism as well as rheumatic disorders in diabetes.

Approach to a Patient with Rheumatic disorders in Diabetes

History taking and Physical examination

1. Duration of Diabetes.
2. Age and other comorbidities.
3. Treatment history and history of compliance to treatment of DM and associated complications.

Physical examination

1. General assessment of diabetic status.

Musculoskeletal examination

1. Joint inspection.
2. Schober's test.
3. Rapid screening and assessment of structure and function of small and large joints and adjoining areas.
4. General musculoskeletal examination-a comprehensive assessment of joint inflammation.

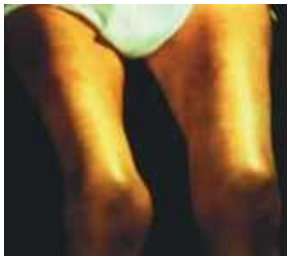
5. Regional musculoskeletal examination – focused assessments of structure, function and inflammation combined with special investigation. Focused neurological assessment of the diabetic patient with 10g monofilament test, vibration sensation testing, ankle jerk reflex, muscular atrophy, abnormal position sense, should be done, for detecting Loss of Protective Sensation (LOPS). LOPS and DSPN (Distal Symmetric Polyneuropathy) are major risk factors for foot ulceration and falls.

Laboratory Investigations

1. Detailed assessment of the patient's diabetic status.
2. Investigation pertaining to rheumatic disorders: ESR, RA factor, Anti CCP antibodies, ANA.
3. Digital X-Rays. Ultrasound, MRI's and other imaging modalities for the affected joints, cytopathology and biochemistry of fluid aspirated from affected joint (to distinguish between septic arthritis and gout).

Musculoskeletal conditions unique to DM

1. **Diabetic sclerodactyly:** This is seen as waxiness and thickening of the skin, especially in the fingers. It resembles scleroderma, however, Raynaud's phenomenon is absent. It may be associated with cheiroarthropathy.
2. **Diabetes amyotrophy:** This usually involves the proximal legs and occurs due to lumbosacral plexopathy with involvement of nerve roots and peripheral nerves. This is likely due to ischemic neuropathy.



Diabetes amyotrophy

3. **Diabetic muscle infarction:** This is a self-limited condition with a very painful swelling with limited range of motion of the involved muscle.
4. **Mononeuritis multiplex:** May occur due to diabetes, due to simultaneous involvement of more than one nerve. This will be associated with pain and motor weakness in the distribution of the affected nerve.

Conditions found with increased frequency with DM

1. **Diabetic Cheiroarthropathy:** Stiffness of the hands with shiny waxy skin, this is common in type 1 DM, patients are asked to perform the prayer sign which shows malalignment of the fingers together.

2. **Trigger fingers, flexor tenosynovitis, Stenosing tenosynovitis:** Occurs as chronic musculoskeletal complications of diabetes, associated with nodule formation and thickening of the flexor tendon or sheath, this can lead to the fingers getting stuck in a flexed position, with sudden snapping straight again (Trigger finger).

Frozen shoulder

This is caused by acute inflammation of the shoulder capsule followed by remodeling and scarring. This is usually seen in elderly patients, more often in women and in patients with diabetic mellitus.

Patients present with shoulder pain and stiffness with limitation of movement, the pain and stiffness are

chronic, lasting for more than 24 months at a stretch. Frozen shoulder is usually diagnosed clinically. Treatment mainly consists of analgesics, sometimes a short course of steroids is prescribed, in addition, physiotherapy and other physical therapies are done for relief.

Diffuse idiopathic skeletal hyperostosis (DISH)

Features include calcification or ossification of ligaments, especially the anterior longitudinal ligament of spine with formation of enthesophytes and osteophytes. This is seen obese older type II DM patients. Symptoms include stiffness of the affected area, with reduced range of motion.

Carpal tunnel syndrome

This is an entrapment neuropathy, usually of the median nerve in between the carpal ligament and other structures of the carpal tunnel. Patients with diabetes are more prone to get carpal tunnel syndrome. Patients present with pain, burning and tingling in the distribution of the median nerve.

Definitive treatment consists of relief of pressure of the median nerve along with orthopedic support to the hand. NSAIDS or steroids may also be used.

Dupuytren's contracture

This is a benign fibrosing disorder of palmer fascia. Occurs commonly in elderly males with alcohol related disorders. Also seen as a musculoskeletal complication in chronic diabetes mellitus. The patient complains of tightness of 4^{th} and 5^{th} digit with nodular cord like thickening of the palmar aspects of these fingers.

Septic arthritis

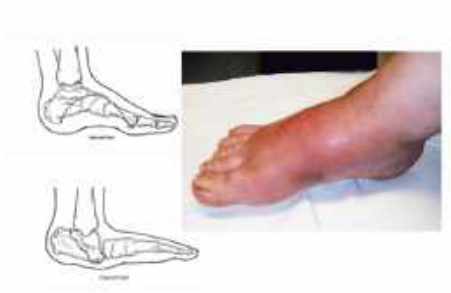
This refers to acute onset inflammatory monoarticular arthritis, often in the large weight bearing joints. Risk factors of septic arthritis include previous joint damage and injection drug use. Immunocompromised situations like advanced age, diabetes mellitus, advanced CKD, immunosuppressive therapies also increase the risk of septic arthritis.

The affected joint is acutely swollen, red and painful. Chills and fever are common. Diagnosis is confirmed by joint fluid aspiration and culture sensitivity. Treatment includes antibiotic therapy along with joint drainage and orthopedic support to the affected joint.

Hammer toe, claw toe deformity, prominent metatarsal heads

This is found with increased frequency in diabetics due to abnormal foot muscle mechanics, motor and sensory neuropathy and structural changes in the foot.

Charcot arthropathy



This is an unusual complication of diabetic neuropathy. The life time prevalence of Charcot's arthropathy ranges from 1-10% in patients with diabetes with increasing prevalence with the severity of neuropathy. Compared to those with type II DM, the patients of type 1DM are younger and have been suffering from diabetes for a longer time and are more prone for this complication. It is a progressive degenerative and inflammatory condition affecting the joints, usually of the foot resulting in ulcerations, deformities, infections and amputations.

The primary pathology lies in progressive sensory and autonomic neuropathy, peripheral arterial disease (PAD), abnormal foot biomechanics and poor wound healing. On this is superimposed repeated trauma and inflammation, leading to the repeated destabilization of the joint.

Eichenholtz classification of Charcot's arthopathy is as follows

1. Stage 0- Prodromal (swollen, hot painful foot)

2. Satge 1-destruction
3. Stage 2 coalescence
4. Stage 3-Consolidation

This is based on clinical and radiological features, of disease progression.

The Sanders and Frybberg classification are based on the anatomical location of the pathology:

Type 1- Involves the fore foot (10-30%)

Type 2- Involves the lisfranc joint (45-50%)

Type 3-involves the midtarsal joint (30-35%)

Type 4- Involves the ankle and subtalar joint (8-10%)

Type 5- Involves the calcaneum (2%)

Clinical presentation

Patients are afebrile with no systemic symptoms. There is usually unilateral lower extremity oedema, erythema and increased warmth. Acute Charcot foot is to be considered in patients with recurrent cellulitis but with no systemic or laboratory findings concerning infection. There is usually history of recurrent hospital admissions due to the chronic waxing and waning of the joint symptoms. Imaging of the joints, in the form of plain radiographs, MRI scans and bone scans help to clinch the diagnosis. Management of Charcot arthropathy involves joint immobilization, and usage of offloading devices such as total contact casts and custom orthotics to redistribute pressure away from vulnerable areas. Drugs such as intranasal salmon calcitonin, denosumab and teriperatide show some promise.

Prevention

Strategies include good glycemic control, regular foot examinations, patient education and self-care practices. Recommendation for foot care include

1. Annual comprehensive foot evaluation to identify risk factors for ulcers and amputations.
2. Individuals with history of sensory loss or prior ulcer should have their feet checked at every visit.
3. All diabetic patients should abstain from smoking and screening for peripheral arterial disease is also essential.
4. General preventive foot care education is essential for all diabetic patients.

Gout

Gout is a chronic painful musculoskeletal disorder which may be seen in association with type II DM and metabolic syndrome. The prolonged hyperuricemia produces recurrent inflammatory arthritis affecting first MTP joint. It can also produce chronic tophi and erosive arthritis. During acute episodes, NSAIDS, steroids or colchicine can be used. Urate lowering drugs are used in the long term.

CONCLUSION

Holistic management of Diabetes is essential for the prevention of complications and controlling the comorbidities. The basic pillars remain diet management and physical activity. Adverse health outcomes of physical inactivity in diabetic patients include musculoskeletal disorders like arthritis and low back ache. Thus, regular physical activity of at least 30 minutes of moderate intensity or 15 minutes of rigorous intensity physical activity may reduce the risk of Type 2DM, blood pressure, cardiovascular disease, as well as promote musculoskeletal health and quality of life.

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Chapter 42

Dentistry in Regular Diabetes Care

Basab Ghosh

INTRODUCTION

In case of diabetes, elevated blood sugar levels can damage many parts of human body specially heart, kidney, eyes, nerves and blood vessels, including our mouth and teeth. Diabetes increases risk of gum disease, cavities and tooth loss, dry mouth, and a variety of oral infections. In other way, poor oral health can make diabetes more difficult to control. Infections may cause stiff rise in blood sugar and require more insulin or tablets to keep it under control. In addition, diabetes can diminish our ability to taste sweets. Although this change may not be noticeable, it can influence our food choices in favor of additional sweeter tasting foods, thereby affecting our dental health, as well as our ability to control diabetes. Constant high blood sugar for a longer period of time caused by diabetes can contribute to progressive damage to the teeth and gums, which may cause tooth loss.

COMMON FEATURES

Plaque: The teeth are covered normally by an invisible film of bacteria, saliva and food particles called dental plaque. The bacteria feed on the sugars and starches in the foods and beverages we consume and subsequently produce acids that damage the hard enamel coating of our teeth. Higher blood sugar that accompanies diabetes gives the bacteria a greater supply of sugars and starches, leading to production of even more acid. Thus, damage from this acid increases the risk of tooth decay, known as cavities.

Gum disease: If dental plaques are not removed from our teeth with regular brushing and flossing, it hardens under gum line into a substance called tartar or calculus. It irritates the gums and causes gingivitis. This makes the gums tender, swollen and red, and they may bleed when you brush your teeth. Fortunately, your dentist or dental hygienist can prevent or treat gingivitis by removing tartar during a professional dental cleaning. Here again diabetes plays a crucial role in disease exacerbation. Dentist are thus in a much better position to detect either new onset diabetes or poorly controlled diabetes by looking at the gum of the patients.

Periodontitis: Untreated gingivitis leads to a more serious condition when bacteria infect our gums and the bones around our teeth, which is known as periodontitis. This can cause gums to pull away from our teeth and that make teeth to loosen and even fall out. Gingivitis and periodontitis are the most common oral complications of diabetes. Diabetes predisposes patients to development of severe and progressive forms of periodontal disease, which in turn is a serious concern of present days clinical practice. In case of type 2 diabetes, the risk of developing such dental complications are three times higher comparing with someone who doesn't have diabetes. Diabetes lowers our body's resistance to many infections and slows the healing rate. Several studies suggested that people with gum infections may be at increased risk of cardiovascular disease. The Dental Atherosclerosis Risks in Communities

Study have shown evidence of relationship between periodontal infections and presence of sub clinical atherosclerosis. Researchers have given strong evidences that dental infections are closely associated with coronary atherosclerosis as some local bacterial DNA has been identified in distant atherosclerotic plaques.

Diabetes and periodontitis are supposed to share a common pathogenesis that involves an enhanced inflammatory response that can be observed at the local and systemic level. A number of reviews and studies have proposed mechanisms to explain the relationship, which includes microvascular disease, changes in components of gingival cervicular fluid, changes in collagen metabolism, an altered host response, an altered subgingival flora, genetic predisposition and non-enzymatic glycation. Undoubtedly there are genetic connections to diabetes and periodontitis. However, there is strong evidence of the bacterial and host contributions. In the presence of hyperglycaemia, due to altered inflammatory response there is increased in innate immune responses and periodontal tissue destruction. The inflammatory response is mainly caused by the chronic effect of high plasma glucose and the formation of biologically active glycated proteins and lipids that promote inflammatory responses.

DIABETES AND THE SPECTRUM OF ORAL DISEASE

Our teeth and gums aren't the only parts of our mouth at risk.

The following problems also can occur**:**

Dry mouth: Dry mouth (xerostomia) occurs when our salivary glands don't produce sufficient saliva to keep our mouth moist. Dryness contributes to cavities and gum diseases, because lack of saliva does not help to wash away the bacteria that contribute to these conditions. Dry mouth also causes tissues in our mouth to become inflamed and sore. As chewing, tasting and swallowing become difficult it may reduce our interest in eating, so it can make diabetes control more challenging, since patient may not eat properly to keep blood sugars in control.

Fungal infection: Candida albicans is a fungus that normally lives inside our mouth without causing any problems. But in case of diabetes, deficient saliva in the mouth and extra sugar in the saliva may allow the fungus to cause an infection called candidiasis (thrush), which appears as sore white or red areas in our mouth. Smoking and wearing dentures all day and night increases the risk of thrush. No smoking and limiting the time the dentures are worn both could reduce the risk of getting thrush.

Burning mouth syndrome: When we have this condition, we may feel severe burning and pain in our mouth even though we don't see any problems in your mouth that could be causing it. Dry mouth and candidiasis can cause burning mouth syndrome. Diabetic neuropathy may lead to oral symptoms of tingling, numbness, burning or pain in the oral region.

Dangers of acute oral infection: Any diabetic patient with acute dental or oral infection presents a problem in management of both diabetes and dental care. The dental infection often causes uncontrolled diabetes, and as a result further the infection is not handled by the body's defense mechanism. So infection control has to be aggressive here, along with tight glycaemic control.

Oral surgery and diabetes: Like all surgical procedures here we need cautious handling of the case, as diabetes can complicate surgery. Diabetes retards healing and increases risk of post operative infection. If patient needs oral surgery, they should follow the *American Diabetes Association's recommendations***:**

- **Remind dentist that you have diabetes**. Patient should discuss any problems regarding infections or about controlling blood sugar with the dentist.
- **Eat before your dental visit.** The best time

for dental work is when you know that your blood sugar is in a normal range, which allows for better healing. If your blood sugar level is out of control when you have a dental surgery scheduled, you may need to postpone the procedure until it's in control.

- **Take your usual medications**. Unless your dentist or diabetologist tells you to change your medication schedule, continue taking your medications.
- **Plan for your eating after surgery**. If you are having any dental work done that may leave your mouth sore, plan to eat soft or liquid foods that will allow you to eat without pain. Do not skip a meal to avoid hypoglycemia.
- **Wait until your blood sugar is under control**. It's best to have surgery when your blood sugar levels are within your goal range. If your dental needs are urgent and your blood sugar is poorly controlled, talk to your dentist and diabetes doctor both for better care in a single possible time.

The protocol of regular dental care in a diabetic person should be tighter enough as our mouth is the common source of infection causing concern for disturb glycaemic control. *A diabetic person should follow these steps:*

- Control your blood glucose.
- See dentist at least twice a year, and make sure dentist knows about your diabetes.
- Brush twice a day, using a soft nylon toothbrush. Also clean the tongue.
- Floss every day.
- Look for early signs of gum disease, such as bleeding gums, redness and swelling.
- Inform dentist if dentures (false teeth) do not fit right or if gums are sore.
- Quit smoking.

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CONCLUSION

In view of the relationship between infection, inflammation and cardiovascular disease, way back Howe G.D et al suggested periodontal disease as the sixth diabetic complication, after nephropathy, neuropathy, retinopathy and microvascular and macrovascular complications (5). I personally feel, dentistry should get equal importance in regular diabetes care and management protocol. More information from prospective long-term clinical trials targeted to answer many unanswered questions regarding diabetes and dental problems should help to guide therapy in future. It will have immense impact in reducing additional health related economic burden, potentially preventing diabetes by early case detection at the dentist`s clinic, preventing cardiovascular disease by avoiding or early intervention to periodontitis and other co-morbidities. Awareness among population is the key to success, here it`s applicable too!

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Section 13

Section Editor : **Karuna K Barman & Achintya Pal**

Social Issues in Diabetes

Chapter 43

Behavioural Research & Psychological Issues in Diabetes

Manoj Kumar Gogoi

INTRODUCTION

Diabetes mellitus (DM), encompassing type 1 (T1DM) and type 2 (T2DM), is a global public health concern, affecting over 500 million individuals worldwide, and continues to be one of the top 10 leading causes of death according to the World Health Organisation (WHO) estimates. While diabetes management mainly focuses on pharmacological therapies, diet, and glucose monitoring, behavioural science offers keys to improving adherence, lifestyle modifications, and psychosocial well-being. Moreover, the success of diabetes management depends on how patients act, such as medication taking, diet, exercise, and glucose self-monitoring, and how psychological factors (stress, mood, beliefs) interact with those behaviours. In recent years, increasing research attention has been directed toward the behavioural and psychological comorbidities associated with diabetes. Evidences support psychological and behavioural interventions, including cognitive-behavioural therapy (CBT), psychoeducation, motivational interviewing, and digital health solutions, demonstrates benefits in reducing distress, enhancing self-care, and modestly improving glycaemic outcomes, though findings remain heterogeneous.

BEHAVIOURAL ASPECTS IN DIABETES

Understanding the relationship between diabetes and mental health is essential for creating more effective, comprehensive treatment approaches that address both psychological and physiological aspects of these interconnected health issues.

Lifestyle Modification

Lifestyle changes such as dietary modifications, including physical activity, and weight management, are the backbone of diabetes prevention; however, adoption is challenging. It has been proven that self-efficacy, action planning, goal setting, and social support facilitate success in lifestyle change. Trending digital tools (apps, AI tools) are increasingly tested to support adherence, feedback, and motivation.

Treatment Adherence and Barriers

Treatment adherence remains a key challenge of the behavioural barrier in diabetes, leading to suboptimal glycaemic control and increased comorbidities. Motivational deficiencies such as uncertainty and low readiness to change often reduce engagement with lifestyle modification. However, socioeconomic as well as cultural factors such as financial burden, limited resources, lack of education, cultural beliefs, stigma, also contribute to disparities in diabetes management.

Self-monitoring & Self-care Behaviour

Self-monitoring and self-care are key factors in improving adherence to diabetes care. Behaviour-change techniques (BCTs), including reminders, feedback loops, and problem-solving, have now been

identified as "active ingredients" in interventions that influence these behaviours. Among these, social support and goal setting are the most frequently applied BCTs and are consistently associated with improvements in glycaemic outcomes.

PSYCHOLOGICAL ISSUES IN DIABETES

Diabetes Distress

Diabetic distress is related to concern about complications, regimen fatigue, emotional burden, frustrations, and worries about the management of diabetes. More than 30% of individuals with diabetes report clinically significant levels of diabetes distress. Elevated distress levels are linked with poor self-management behaviours, higher HbA1c, and increased risk of complications, while reductions in distress have been shown to improve outcomes. To measure diabetic distress, several different models, including Problem Areas in diabetes PAID, Type 1 Diabetes Distress Scale T1-DDS, and Diabetes Distress Scale DDS, are available. Understanding patient experiences through qualitative research may therefore provide deeper insights into the mechanisms underlying diabetes distress, inform the development of more comprehensive assessment tools, and enhance patient–clinician communication by fostering more empathetic and person-centred care.

Depression & Anxiety

Depression has well-established bidirectional relationship with diabetes as depression increases the risk of incident diabetes, while diabetes itself predisposes to depression through disease burden and complications. However, handling either condition is critical, highlighting the need for integrated management strategies to improve patient adherence. Such strategies require collaboration across multiple healthcare disciplines, including endocrinology, psychiatry, and primary care, to offer a holistic approach to patient care.

Anxiety contributes to poor adherence, enhanced diabetes distress, and poor quality of life, emphasising the need for routine screening and integrated psychological support in diabetes care.

Eating Disorders

It often exists in different ways which is a severe risk in individuals with type 1 diabetes. Disordered behaviours, including binge eating and rigid dieting, are also more frequently observed in this population. This coexisting challenge of eating disorders and diabetes mellitus necessitates a comprehensive approach that includes psychotherapy, glycaemic control, nutritional counselling, and diabetes education.

Fear of Hypoglycemia

Fear of hypoglycemia is defined as a specific extreme fear triggered by the risk or occurrence of hypoglycemia and reported by up to one-third of individuals with diabetes. People often worry about losing consciousness in public, causing an accident or injury, experiencing emotional instability or irritability, and facing socially embarrassing situations. This results in maladaptive behaviours, such as insulin withholding, avoiding exercise, and intentionally maintaining high blood sugar levels. To prevent diabetic distress and enhance quality of life, early detection with validated tools (e.g., HFS-II) and interventions like structured education, continuous glucose monitoring, and cognitive-behavioural therapy are effective.

Cognitive Impairment & Dementia

Type 2 diabetes confers a 1.5–2 fold higher risk of cognitive decline and dementia, driven by hyperglycaemia, insulin resistance, vascular injury, and recurrent hypoglycemia. Cognitive impairment compromises self-care and glycaemic control, highlighting the need for routine screening, simplified regimens, and caregiver support in older adults.

BEHAVIOURAL RESEARCH & INTERVENTION EVIDENCE

Table 1 highlights primary studies on behavioural in diabetes, showing benefits of CBT and iCBT in reducing distress, depression, and fear of hypoglycemia. However, limitations this trial were limited by small sample sizes, short duration, heterogeneity, and lack of cultural adaptation, with HbA1c often listed as the main outcome while psychological endpoints remain secondary.

Table 1: Primary Studies on Psychological Issues in Diabetes

Issue	Design	Key Highlights	Reference
Diabetes Distress	RCT	Group CBT ↓ distress, ↓ HbA1c (T2DM)	Tunsuchart K, et al. 2020.
Depression	RCT	CBT ↓ depression & distress (T2DM)	Abbas Q, et al. 2023.
	RCT	iCBT ↓ depression, ↑ QoL (T1DM)	Carreira M, et al. 2023.
Fear of Hypoglycemia (FoH)	RCT	CBT (FREE) ↓ FoH, ↑ self-care (T1DM)	Martyn-Nemeth P, et al. 2024.
	Cross-sec	FoH ↑ HbA1c, ↓ QoL (T1DM)	Mesa Diaz AM, et al. 2025.
Eating Disorders	Cross-sec	Disordered eating ↑ distress & FoH (T1DM)	Priesterroth LS, et al. 2025.
Cognitive Impairment	Cross-sec	37% elderly T2DM impaired; HbA1c ↑ risk (T2DM)	Khan F, et al. 2025.
Cognitive Decline	Cross-sec	Poor control & duration ↓ cognition (T2DM)	Kinattingal N, et al. 2023.

RCT – Randomized Controlled Trial; Cross-sec – Cross-sectional; CBT – Cognitive Behavioral Therapy; iCBT – Internet-based Cognitive Behavioural Therapy; FoH – Fear of Hypoglycemia; HbA1c – Glycated Hemoglobin; QoL – Quality of Life; DEB – Disordered Eating Behaviours; ↑ increase; ↓ decrease.

Social & Cultural Context

Diabetes self-care efficacy is strongly depended on social and cultural factors, as represented in . The major factor includes socioeconomic barriers, social stigma, health system constraints and family support. Limited education and resources often hamper diabetes self-care, while supportive family involvement can greatly enhance adherence. Hence, recognizing and addressing such factors are crucial as these impacts both sustainable and sensitive to patient needs, ultimately improving long-term health outcomes and quality of life.

Special Populations

Children & Adolescents with Type 1 Diabetes

In this year, the American Diabetes Association (ADA) issued updated recommendations on the care of children and adolescents with type 1 diabetes. An adolescence is vulnerable period for psychosocial development, peer pressure, and desire for autonomy, all of which can conflict with parents or

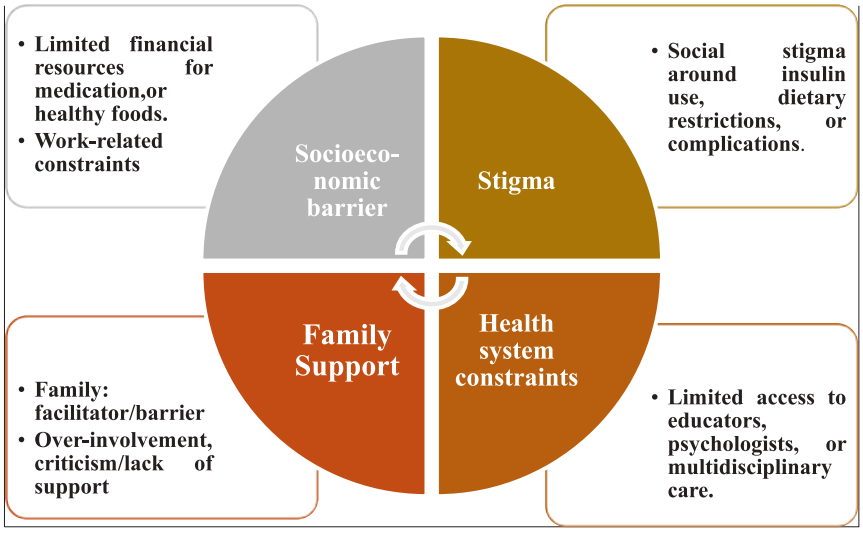


Figure1 : Key social and cultural factors impacting behavioural and psychological outcomes

caregivers regarding treatment responsibilities. These can further progress to lead psychological issues such as depression, anxiety, and eating disorders.

Elderly Population

Elderly population face a high disease burden of comorbidities along with psychological issues. Factors such as social isolation, functional decline, loss of independence, and fear of hypoglycemia increase susceptibility to depression and anxiety, however, prolonged disease duration and poor glycaemic control contribute to cognitive decline and dementia risk. Hence, it is advised to prioritize simplified regimens, routine cognitive screening, and psychosocial support to address depression, anxiety, and cognitive decline in the elderly.

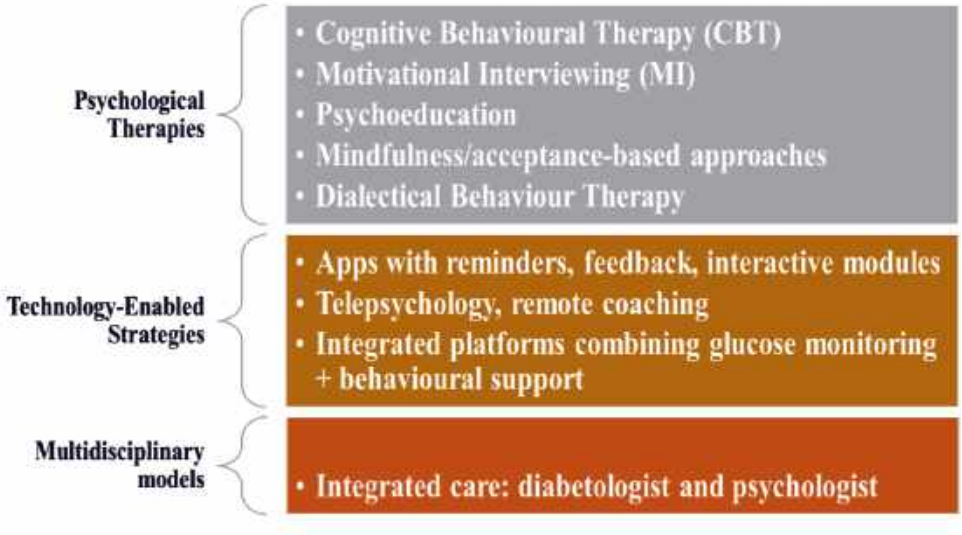
Women with Gestational Diabetes Mellitus (GDM)

Women with GDM, often suffer with unique psychological stressors (worry about fetus, postpartum changes) and behavioural challenges (diet, weight regulation). Factors such as sudden diagnosis, strict lifestyle modifications, and fear of adverse maternal–fetal outcomes can worsen the levels of stress, anxiety, and depressive symptoms. However, due to poorer adherence to dietary recommendations, reduced physical activity, and suboptimal glycaemic control, increases risks for both mother and child.

INTERVENTIONS & STRATEGIES

A variety of management strategies of diabetes in terms of Behavioural and psychological interventions is represented in . Cognitive Behavioural Therapy (CBT), motivational interviewing, psychoeducation, and mindfulness-based approaches have been shown to enhance adherence along with decrease in diabetes distress. Recently, technology bases strategies like android apps for reminders feedbacks, counselling, websites, and integrated platforms combining glucose monitoring with behavioural support reported to offer scalable and accessible solutions. Prominently, integrated care models where diabetologists collaborate with psychologists is recommended for comprehensive diabetes management, as they simultaneously address metabolic control,

Figure2 :Behavioural and psychological interventions in diabetes management



psychological well-being, and patient adherence, ultimately leading to improved quality-of-life outcomes.

CONCLUSION

Diabetes, metabolic disorder, coexisting with psychological issues has become a growing disease burden, where prompt early recognition is key factor to influence self-care, treatment adherence, and long-term outcomes. Psychological issues like distress, depression, anxiety, eating disorders, and cognitive decline impair effective diabetes management. Integrated management strategies including, CBT, psychoeducation, and digital health tools reported to beneficial in terms of both clinical outcomes and mental well-being. It is therefore advised to incorporate routine psychosocial screening, patient-centred care to achieve optimal outcomes in individuals with diabetes.

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Chapter 44

Religious Fasting and Glycemic Management

Anirban Majumder

INTRODUCTION

Religious fasting, a practice deeply rooted in spiritual and cultural traditions, poses unique challenges and opportunities for glycemic management in individuals with diabetes. The physiological alterations induced by fasting—ranging from changes in circadian rhythms to shifts in nutrient availability—require careful adaptation of medical nutrition therapy, pharmacologic regimens, and patient education. This review summarizes evidence-based strategies for optimizing glycemic control during various religious fasts, with a focus on Islam (Ramadan), and Hinduism.

Fasting has been an integral component of many religious traditions for millennia, serving as an act of spiritual purification, self-discipline, and communal solidarity. However, for individuals with diabetes mellitus, particularly those on insulin or insulin secretagogues, fasting presents significant risks, including hyperglycemia, hypoglycemia, and dehydration.1 Both hypoglycemia and hyperglycemia are recognized risks, especially when food intake, medication timing, and physical activity patterns are abruptly modified. Thus, physicians must balance respect for religious beliefs with the need for medical safety.

PHYSIOLOGICAL EFFECTS OF FASTING ON GLUCOSE METABOLISM

During fasting, hepatic glycogen stores are depleted within 12–24 hours, prompting gluconeogenesis from amino acids, lactate, and glycerol. Insulin levels decline, while glucagon, cortisol, and catecholamines increase, mobilizing energy reserves mostly from adipose tissue. In individuals with diabetes, this adaptive mechanism can be exaggerated or dysregulated, leading to glycemic instability.

The major risks of religious fasting for individuals with diabetes include hypoglycemia , hyperglycemia, and dehydration & Ketoacidosis. It can also lead to more severe condition like hyperosmolar hyperglycemic state.

Hypoglycemia: Common among insulin-treated or sulfonylurea-treated patients, especially when caloric intake decreases but medication doses remain unchanged.

Hyperglycemia: May occur due to excessive carbohydrate intake during non-fasting hours, reduced insulin adherence, or counter-regulatory hormone excess.

Ketoacidosis: Risk increases in patients with type 1 diabetes or those on SGLT2 inhibitors, particularly during prolonged fasts or dehydration.

RELIGIOUS FASTING TRADITIONS AND THEIR IMPLICATIONS

1. Hindu Fasting Practices: Hindu fasting varies widely—from complete abstinence to selective

exclusion of foods such as grains or salt (e.g., Ekadashi, Navratri). Fasting durations range from a few hours to several days.

Management Strategies:

- Encourage intake of low-glycemic index foods such as fruits, nuts, and milk during permissible meals.
- Monitor blood glucose regularly, even on fasting days.
- Dose adjustment of medications: basal insulin may be reduced by 20–30%, while bolus insulin shifted to Iftar and Suhoor.
- Prefer long-acting GLP-1 receptor agonists or DPP-4 inhibitors due to low hypoglycemia risk.
- Encourage balanced Iftar meals, hydration, and avoidance of sugary beverages.
- Continuous glucose monitoring (CGM) is safe and recommended.

PHARMACOLOGIC CONSIDERATIONS DURING FASTING

Drug Class	Adjustment	Recommendation	Comments
Metformin	Usually safe	Take with meals	Minimal risk of hypoglycemia
DPP-4 inhibitors	Safe	No dose change	Preferred oral agents
GLP-1 receptor agonists	Safe	No dose change	May reduce appetite and improve postprandial control
SGLT2 inhibitors	Use cautiously	No dose change	Risk of dehydration and euglycemic DKA
Sulfonylureas	Use cautiously	Reduce or withhold morning dose	Use short-acting agents if required
Basal insulin	Use cautiously	Reduce dose by 15–30%	Monitor fasting glucose daily
Bolus insulin	Use cautiously	Shift to evening meals	Individualize based on glucose monitoring

- For insulin-treated patients, basal insulin may be continued with minor (10-20 %), dose reduction.
- Avoid prolonged fasting in patients with brittle diabetes, pregnancy, or chronic kidney disease.

2. Islamic Fasting (Ramadan): Ramadan fasting entails abstaining from food, drink, and oral medications from dawn (Suhoor) to sunset (Iftar). The fast may extend up to 16 hours depending on the time of the year. Multiple studies, including the EPIDIAR study,1 have reported increased rates of severe hypoglycemia during Ramadan among individuals with type 2 diabetes.

Management Strategies:

- Pre-Ramadan assessment of glycemic control and complications.

PRE-FASTING ASSESSMENT AND PATIENT EDUCATION

A pre-fasting medical assessment and a structured education program are crucial for all diabetic patients who plan to fast. The following components should be addressed:

1. Medical Assessment – Evaluate glycemic control (HbA1c), comorbidities, and prior hypoglycemia episodes.

2. Risk Stratification – Classify patients into low, moderate, or high risk based on the IDF-DAR (International Diabetes Federation–Diabetes and Ramadan) guidelines.

3. Dietary modifications: Patients should be advised to limit high-fat and high-carbohydrate foods typically consumed during Ramadan, as a major study on this topic noted improvements in blood glucose and BMI with careful planning.
4. Education – Cover topics such as self-monitoring, meal planning, symptom recognition, and when to break the fast.

5. Monitoring – Encourage frequent SMBG or CGM use; breaking the fast if glucose <70 mg/dL or >300 mg/dL.

Risk Stratification:

A. Low risk: People with diabetes considered to be at low risk and may be allowed to fast, include:

Type 2 diabetes not treated with either insulin or sulfonylurea agents
Type 2 diabetes treated with basal insulin

B. People with diabetes considered to be very high risk and are advised not to fast include:

Type 1 diabetes with suboptimal glycaemia
Episode of DKA or HHS 3 months prior to Ramadan
Recurrent hypoglycaemia or hypoglycaemic unawareness
Severe or recurrent hypoglycaemia 3 months before Ramadan on existing regimen
Pregnancy with pre-existing diabetes
Acute illness or Stage 4–5 chronic kidney disease
Advanced macrovascular complications or advanced age with ill health

EMERGING EVIDENCE AND TECHNOLOGIES

Digital glucose monitoring, smart insulin pens, and telemedicine have revolutionized religious fasting management. Studies using CGM during Ramadan demonstrate improved time-in-range with individualized dose adjustments. Artificial intelligence–assisted prediction models are under exploration for fasting glycemic safety. Management should be tailored to the individual's specific needs and medical history.

CONCLUSION

Religious fasting presents a complex interplay between spiritual conviction and metabolic physiology. With careful pre-fasting assessment, patient education, and tailored therapeutic adjustments, most individuals with diabetes (specially people at low risk) can fast safely. The key lies in proactive planning, continuous monitoring, and culturally informed clinical guidance.

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Chapter 45

Psycho-socio-economic impacts in the knowledge and practice of intermittently scanned continuous glucose monitoring (CGM) vs real time CGM

Rebecca John
Nitin Kapoor

INTRODUCTION

The incidence of diabetes mellitus has been gradually increasing over the last few decades. With an estimated prevalence of 10.5%, India remains a hotspot for this non-communicable disease. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glucose control results in lower rates of microvascular complications. Hence, regular monitoring of blood glucose levels and titration of insulin remains critical to avoid untoward outcomes.

The traditional method of self-monitoring of glucose levels (SMBG) is by handheld glucometers using finger-prick capillary blood. Pain associated with multiple daily pricks, inability to monitor glucose trends, and inconvenience of carrying the glucometer remain limiting factors to this approach. Advancements in technology have introduced novel glucose monitoring devices, which have eased out monitoring as well as enabled subjects to self-manage their blood glucose levels; thereby revolutionizing the management of diabetes mellitus.

CGM DEVICES

A continuous glucose monitoring (CGM) device includes a glucose sensor that continuously measures interstitial fluid glucose concentration, an electronic processing unit that communicates with the sensor, and a data display unit. Healthcare professionals can use either an intermittently scanned CGM (is-CGM), also known as a flash glucometer, or a real-time CGM (rt-CGM). With its-CGM, data capture is initiated by the user, and a sensor is scanned to view and store the readings. These usually do not have automatic alarms in them; however, some of the newer versions may have this feature. In contrast, the rt-CGM continuously measures and displays glucose levels. The RT-CGM system is equipped with additional functionalities, including alerts for both low and high glucose levels.

Several studies have demonstrated a beneficial effect of CGM on glycemic profile among those with type 1, type 2, and gestational diabetes mellitus, with higher efficacy for rt-CGM in comparison to is-CGM being reported among type 1 diabetes mellitus. The American Diabetes Association (ADA) Standards of Care published in 2025 recommends the use of rt-CGM or is-CGM for youth and adults with diabetes mellitus on insulin therapy. However, its integration into the community with this perspective remains sub-optimal. Furthermore, data from the type 1 diabetes exchange registry demonstrated a poor adherence to CGM, with 41% discontinuing the same after 1 year.

Challenges reported with CGM use include discomfort related to sensor insertion, skin reactions to the sensor, multiple alerts and alarms leading to alarm fatigue, depression, anxiety, fear of hypoglycemia, impaired sleep, and quality of life. In India, economic constraints also play a role and hinder the adoption of CGM into routine clinical practice. In this article, we review the psychosocial

and economic impacts of the practice of rt-CGM and is-CGM.

PSYCHOSOCIAL ASPECTS OF CGM USE

It remains key to understand that there are limited studies on the psychological aspects of using CGM. The impact of rt-CGM and is-CGM on psychological outcomes in individuals with diabetes mellitus and caregivers remains controversial. There are no direct head-to-head comparison studies that have looked at the psychological aspects among users of rt-CGM and is-CGM as a whole.

1. Quality of Life (QOL)

There is varying data on the quality of life among those on rt-CGM and is-CGM. A multicentre randomized controlled trial aimed to assess the impact of CGM on QOL among children and adults with type 1 diabetes. 451 individuals were randomly assigned to receive CGM or to the control group, where they practised SMBG. The quality of life assessed at 26 weeks did not show any significant improvement with rt-CGM. However, it is interesting to note the baseline QOL scores were high in this study. Glocker et al from Switzerland looked at quality of life scores among children with type 1 diabetes mellitus and their parents between those on rt-CGM and is-CGM. They identified no difference between QOL questionnaire scores among the children in these 2 groups. However, among parents of these children, those on is-CGM had a lower QOL, which correlated with the increased scanning frequency. A meta-analysis carried out by Franceschi et al, which looked at QOL with both is-CGM and rt-CGM in youth, suggested an improvement among both children as well as their parents. The data on quality of life comparing rt-CGM and is-CGM are conflicting, and larger studies are needed for assessment of the same.

2. *Fear of hypoglycemia (FOH)*

Rt-CGMs have alerts for hypoglycemia. Hence, it is expected that those using these devices may tend to feel more secure and have less FOH. Reddy M et al randomized 40 adults with type 1 diabetes mellitus to rt-CGM or is-CGM to compare time in hypoglycemia. They demonstrated a lower time in hypoglycemia as well as FOH among those using rt-CGM. The study by Glocker et al demonstrated no difference in FOH between the two groups using rt-CGM or is-CGM. However, parental FOH was more among those with children on is-CGM. Finally, while some studies have suggested a reduction in FOH, others have even suggested no change or even an increase in fear of hypoglycaemias with continuous glucose monitoring.

3. *Depression and anxiety*

Rt-CGM using adolescents may exhibit more depressive symptoms. Trials have suggested a possible association between decreased time in range and depressive feelings. With regards to anxiety, studies assessing anxiety among rt-CGM users are scanty with small sample size. Burckhardt et al aimed to assess anxiety levels in parents of children aged 2-12 years with type 1 diabetes mellitus and noted lower anxiety with rt-CGM use compared to SMBG. Moreover, data on is-CGM and depression or anxiety are absent.

4. *Alarm fatigue*

Alarms are present with rt-CGMs which are designed to alert when glucose levels rise or fall beyond a specific threshold, trend to these patterns or when there are drastic changes in blood glucose levels. Is-CGMs are usually not equipped with these alarms, except for a few newer devices. Safe and widespread use of rt-CGM is limited by alarm fatigue, a state where an individual receives multiple alerts and stops responding appropriately. With rt-CGMs; patients have reported annoyance with alerts for elevated glucose levels while finding it useful when signalling hypoglycaemia. The disturbance and embarrassment caused to the individual by alarms at school or the workplace needs to be considered as well. With is-CGMs, most models do not have alarms and hence the individual is alerted of hypo- and

hyperglycaemias only on user-initiated scanning, reducing fatigue and sense of overwhelm.

5. *Sleep quality*

Whether the quality of sleep is improved by rt-CGM is unclear. Some studies have suggested improvement and others no difference with its use. While a lower FOH may exist among those on rt-CGMs enabling better sleep quality, the role of false alarms or alerts on trends to hyper and hypoglycemia may increase night-time awakening. Data on sleep quality with is-CGMs as well as comparison studies are lacking.

6. *Behaviour change and Empowerment*:

Due to the continuous nature of data available from rt-CGM, a more proactive behaviour by the user is encouraged. Rt-CGMs aid in the dynamic adjustment of diet, physical activity, and insulin administration by promoting behavioural changes in response to blood glucose patterns. The ability to see immediate consequences of their actions with rt- CGM provides a sense of empowerment in this group. Is-CGM, which provides only retrospective or on-demand input on glucose levels, may miss out a few values and hence has a lesser opportunity for guiding immediate management.

7. *Family support:*

CGMs both is-CGM as well as rt-CGM may reduce familial conflict with regards to diabetes management and overall diabetes distress. However, this has not been demonstrated in all studies. Real time data sharing is an option with rt-CGM, increasing the safety for those at high risk for fluctuations in blood glucose profile; particularly younger children and elderly. Often, the data is shared with a health care professional as well as a family member allowing for collective decision making. There is a chance that this type of sharing might be perceived as intrusive and lead to concerns among adolescents about losing their independence. No option for data sharing exists with is-CGM devices.

ECONOMIC FACTORS

The substantial cost of CGMs creates a financial challenge for its longterm use. CGMs have been proven cost effective if it can reduce complications related to diabetes mellitus. By mitigating episodes of hypoglycemia, particularly severe instances necessitating medical intervention, as well as reducing hyperglycemic emergencies such as diabetic ketoacidosis; rt-CGM has the potential to decrease hospitalizations, emergency interventions, and long-term complications. These outcomes can lead to significant cost savings. While is-CGM also demonstrates advantages over traditional fingerstick methods in numerous studies, it may not perform as effectively as rt-CGM in acute scenarios. Rt-CGMs are costlier than is-CGM, however both remain inaccessible for a significant proportion of the population with diabetes mellitus in India. The cost-utility has been studied in countries such as Denmark with rt-CGM projected to be highly cost effective compared to is-CGM which in turn remains more cost-effective than SMBG among individuals with type 1 diabetes mellitus on multiple daily injections. In countries like India, with minimal insurance coverage for CGMs; further studies are needed to understand the cost-benefit and in particular how this would vary between the different socioeconomic strata as well as between rural and urban population.

CONCLUSION

In summary, it is essential to recognize that both diabetes itself and the technologies employed in its management can be linked to negative emotional experiences, potentially exacerbating anxiety and adversely affecting psychological outcomes. Further studies are needed to completely understand the psychological effects of these devices among individuals with diabetes mellitus and their caregivers. While the clinical effectiveness of the is-CGM and rt-CGM has been unequivocally proven, addressing the psychosocial barriers and high costs associated with their use is crucial for ensuring their widespread and compliant adoption in the future.

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Section 14

Section Editor : **Manash Pratim Baruah**

Emerging Technologies and Therapeutics in Diabetes

Chapter 46

Insulin Pumps And Automated Insulin Delivery Systems

Nilanjan Sengupta
Roohi Nanda

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic conditions worldwide, affecting more than 500 million individuals, with projections suggesting a further rise in the coming decades. While type 2 diabetes mellitus (T2DM) accounts for the majority of cases, type 1 diabetes mellitus (T1DM) represents a distinct challenge because it requires lifelong insulin therapy from the time of diagnosis. Insulin remains the only effective therapy for patients with absolute insulin deficiency, yet the traditional mode of administration through multiple daily injections (MDI) is often inadequate to achieve optimal glycemic targets. Physiological insulin secretion is characterized by a dynamic basal secretion with rapid surges in response to meals. In contrast, MDI regimens, which rely on fixed long acting insulin for basal coverage and bolus doses before meals, frequently fail to replicate this fine-tuned pattern.

The shortcomings of conventional injection- based therapy, including the risk of hypoglycemia, glycemic variability, and the burden of frequent injections, have driven continuous efforts to develop improved delivery strategies. Arnold Kadish has been widely credited for formulating the first automated or closed-loop insulin delivery system in 1964. He used an on-off control system to connect continuous real- time intravenous glucose measurements to two intravenous syringe pumps containing insulin and either glucose or glucagon to maintain target range glycemia. The first portable AID or closed- loop system was developed by Shichiri and colleagues in Japan in 1984. The advent of continuous subcutaneous insulin infusion (CSII), more commonly referred to as insulin pump therapy, represented a major step forward. Pumps allow programmable basal rates and flexible bolus dosing, thereby more closely resembling physiological secretion. More recently. Their use has been associated with improvements in glycated hemoglobin, increased time- in- range (TIR) glucose, reduction in hypoglycemic episodes and improvement in quality of life. However, despite strong clinical evidence, adoption remains limited in low and middle- income countries due to cost, accessibility, educational barriers and paucity of technical support. The integration of pumps with continuous glucose monitoring (CGM) and computer algorithms has enabled AIDs, also known as hybrid closed- loop or artificial pancreas systems. These have marked a paradigm shift in the management of diabetes mellitus.

INSULIN PUMPS: PRINCIPLES AND EVOLUTION

Insulin pumps deliver rapid- acting insulin analogues continuously via a cannula placed in the subcutaneous tissue. The basal rate can be programmed to vary at different times of the day and night, reflecting diurnal variations in insulin sensitivity. Meal- related boluses can be administered at the touch of a button, with modern

pumps often incorporating bolus calculators that take into account carbohydrate intake, pre- meal glucose and insulin sensitivity factors. Insulin pumps use only rapid- acting insulin analogues which tends to minimize the risk of delayed hypoglycemia.

In 1970s the insulin pumps were bulky, used a metal needle, had a comparatively short battery life, little flexibility in rate of insulin delivery, but 1990s and

Evidence supporting the use of insulin pumps is well established. Meta- analyses comparing pump therapy with MDI in T1DM patients has consistently demonstrated modest but significant improvements in glycemic outcomes. Pickup and Sutton reported a reduction in glycated hemoglobin by 0.3 to 0.5 percentage points using insulin pumps, compared with MDI, with a parallel reduction in severe

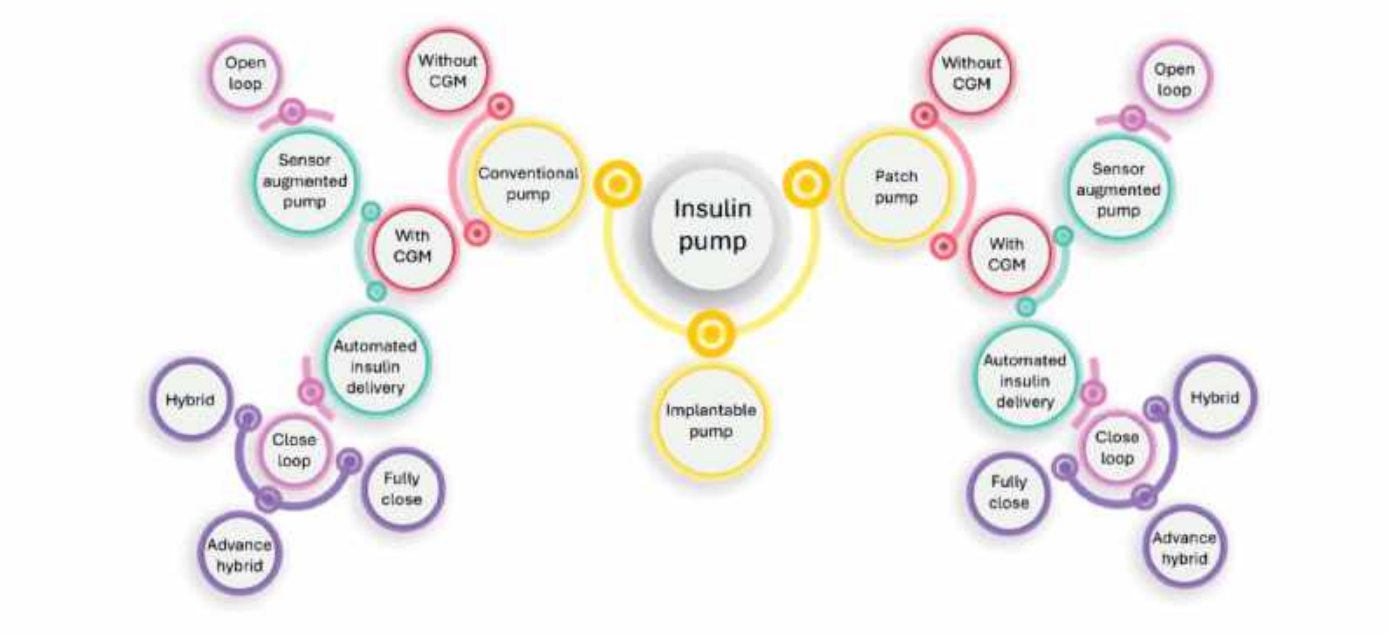

Figure 1: Classification of insulin pumps

2000s saw a revolution in the development of insulin pumps. The miniaturization and advances in electronics have produced compact, portable and user- friendly pump devices. Safety features such as alerts for infusion set occlusion and low battery or low insulin reservoir were integrated alongside longer- life batteries and plastic catheter infusion sets. The current pump devices can store extensive data, connect wirelessly with smart phones or cloud-based system, and even integrate with CGM devices. Tubeless patch pumps have further enhanced convenience by eliminating external tubing and adhering directly to the skin. These innovations reflect a broader trend in diabetes technology towards personalization, connectivity and real- time data sharing between patients and clinicians.

hypoglycemia. The Cochrane review by *Misso et al*. confirmed that insulin pumps provide a superior metabolic control, particularly in children and adolescents. Insulin pumps confer various advantages in terms of glycemic variability and patient satisfaction. Insulin pumps accommodate variations in insulin sensitivity due to circadian rhythms, physical activity or any illness. Patients report greater flexibility in meal timing, reduced injection burden and improved psychosocial well-being when using pump therapy. Its use is not limited to T1DM, can be given to selected patients with insulin- requiring T2DM, particularly those requiring high-dose of insulin, those with glycemic variability, or those unable to achieve targets despite optimized MDI regimens. Studies have shown that

pumps can improve glycated hemoglobin and reduce total insulin requirements in such populations, though widespread use remains limited by cost, availability and paucity of technical support.

AUTOMATED INSULIN DELIVERY SYSTEMS

The integration of insulin pumps with CGM has paved the way for AID systems. These systems consist of three essential components: a CGM, an insulin pump and a control algorithm. The CGM measures the interstitial blood glucose every few minutes and transmits the data to the algorithm. Based on the input, the algorithm adjusts the pump's basal insulin delivery in near real- time. The goal of AID is to maintain the blood glucose levels within the target range, typically 70-180 mg/dl. AID systems utilize a sophisticated controller algorithm that continuously adjusts insulin delivery in response to real- time sensor glucose levels, residual insulin action and other inputs like meal intake, exercise announcement. Several types of control algorithms have been developed which include model predictive control (MPC), proportional integral derivative (PID), and fuzzy logic (FL) controllers. The algorithms accommodate variability of insulin requirements between and within individual users. Despite significant advances in controller algorithms, users still have to manually announce carbohydrate intake to achieve adequate postprandial insulin coverage. This is needed as current hybrid systems are not physiologic, rely on subcutaneous glucose signal which usually has a lag time of 4-10 minutes and hence a delay in the subcutaneous insulin delivery into circulation. Fully AID systems, which obviate the need for carbohydrate counting and manually initiated prandial boluses, are under development.

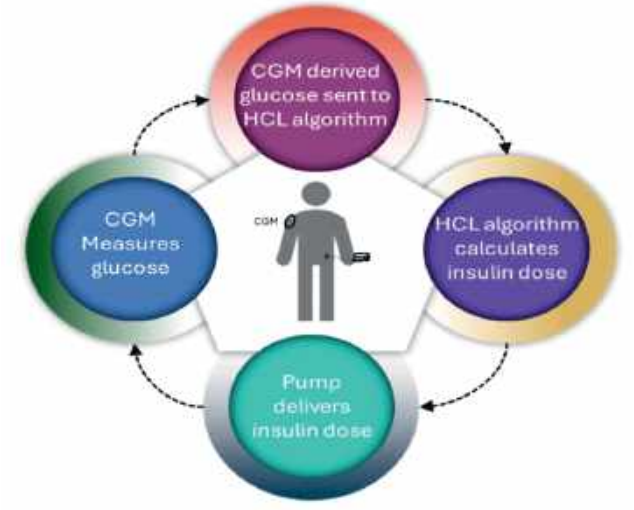

Figure 2: Illustration of the working mechanism of an advanced hybrid closed- loop pump

Table 1: Summary of recommendations: target population for AID system as per American Diabetes Association (ADA) 2025

- Strongly consider recommending to all people with T1DM to improve glycemic control:
  - School- aged children (7-14 years)
  - Adolescents/ adults
- Consider recommending to:
  - Older adults (above 65 years)
  - Pre-school children (<7 years)
  - People with moderate/severe hypoglycemia and hypoglycemia unawareness
  - Pregnancy women with T1DM
  - People with comorbidities: chronic renal failure and gastroparesis
- Consider recommending appropriate AID systems to people with other types of diabetes treated with intensive insulin therapy (multiple daily injections or pump therapy):
  - People with T2DM
  - People after pancreatectomy
  - People with cystic fibrosis
- Use of AID under supervision should be allowed in hospital settings if not contraindicated by clinical status or treatment needs

Currently all commercially available AID systems

(Medtronic 670G/770G, Medtronic 780G, CamAPS FX, Diabeloop, Control-IQ, Omnipod 5 and others) are single hormone (insulin only) systems, dual hormone systems (glucagon and pramlintide), to closely mimic pancreatic physiology, are under development. Pramlintide is an amylin analogue which is co-secreted with insulin from beta cells, tends to reduce postprandial glucose excursions by slowing the gastric emptying and by suppressing glucagon secretion. AID systems currently available in India are Medtronic MiniMed 780G and 640G.

Clinical trials have demonstrated several benefits of AID systems, Brown and colleagues showed that hybrid- loop therapy increased the TIR by 11 percent compared to standard therapy, equivalent to more than two and a half hours additionally spent in target range. Other several trials with systems like Control-IQ and MiniMed 780G have confirmed improvement in glycated hemoglobin, reduction in hypoglycemic episodes and higher patient satisfaction. These benefits have been consistent among all age groups.

LIMITATIONS AND CHALLENGES

Both insulin pumps and AID systems face significant barriers to widespread adoption. The foremost challenge is the cost. Insulin pumps are expensive devices, and the recurring costs of infusion sets, reservoirs, sensors, and calibration supplies add substantially to the financial burden. In high-income countries, insurance coverage often offsets these expenses, but in low- middle income regions, like India, coverage is limited, and out-of-pocket costs make pumps inaccessible to most patients.

Second major challenge is the need for patient education and motivation. These systems require active engagement in diabetes self- management, including carbohydrate counting, troubleshooting device issues, and understanding insulin sensitivity factors. Skin irritation at infusion or sensor sites, occasional device malfunctions, and alarms may contribute to user fatigue. Healthcare infrastructure also influences adoption. Clinicians and diabetes educators require training to interpret pump and CGM data effectively in order to adjust the therapy. Structured diabetes programs are essential to motivate patients to transition from injections to pump- based therapy.

In India, the prevalence of T1DM and T2DM in young, is increasing and so is the need for insulin pumps and AID systems, as they offer a good glycemic control, minimize hypoglycemic episodes and several other advantages. The two major barriers being cost and lack of awareness by both patients and physicians. Nevertheless, there are encouraging developments like increased availability of CGM devices, greater exposure through specialized diabetes centers, and growing recognition of psychosocial benefits of advanced modern technology. With the increase in local manufacturing and decline in cost, it may help broader population accessibility in India.

FUTURE DIRECTIONS

The future of insulin delivery is closely tied to further automation, miniaturization, and integration. Fully closed- loop systems that eliminate the need for meal boluses are already in advanced stages of clinical development, with early trials showing promising results. Controller algorithms are becoming more sophisticated, capable of learning individual patient patterns and adapting insulin delivery dynamically. Bi-hormonal systems that combine insulin with glucagon or with amylin analogues, may provide more physiological control and may further reduce the risk of hypoglycemia. Sensor technology continues to advance, with newer CGM devices offering greater accuracy, longer wear times, and factory calibration that eliminates the need for finger-stick validation. The integration of pumps and CGM with smartphone applications and cloud- based analytics enable remote monitoring by health care providers. These developments also support telemedicine, allowing clinicians to adjust therapy based on real- time data.

CONCLUSION

Insulin pumps and AID systems represent a major advancement in the management of diabetes mellitus. These devices closely replicate the physiological insulin secretion, leading to improvement in glycemic control, reduction in hypoglycemia and improved in quality of life, compared to the conventional multiple daily injection regimens. Although several barriers related to cost, education, availability and infrastructure currently limit widespread adoption, ongoing innovations and a growing evidence base support their increasing role in clinical practice. In India and other resource constrained settings, efforts must focus on affordability, awareness and training to ensure equitable access. The promise of insulin delivery technology lies not only in its ability to transform individual lives but also in the potential to reshape diabetes care on a global scale.

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Chapter 47

AI Driven Blood Glucose Prediction and Personalized Insulin Dosing

Indira Maisnam

INTRODUCTION

Individuals with diabetes requiring intensive and complex insulin regimen (Type 1 and many with Type 2) need multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII). With challenging work schedules, exercise routines and meal patterns they may encounter difficulties in deciding the accurate insulin doses. These difficulties lead to periods of hypoglycemia as well as periods when the blood glucose is above the target range. Hypoglycemia itself sets the stage of recurrent hypoglycemia by causing a functional autonomic failure in the form of hypoglycemia associated autonomic neuropathy (HAAF). Optimal glucose monitoring and insulin dosing is a key component to mitigate these issues. The optimum management of diabetes mellitus on intensive insulin regimen requires accurate blood glucose monitoring and dynamic insulin dosing. Modern continuous glucose monitors (CGM) provide glucose trends facilitating appropriate dose adjustments. Machine learning algorithms including neural networks and gradient boosting enhance CGM utility by prediction of blood glucose and preventing potential glycemic derangement. In type 1 diabetes (T1D) patients using CGM, this approach demonstrated HbA1c reduction of 0.4-1%, increased time in range by 5-10%, and reduced hypoglycemia. Models like run-to-run (R2R) and R2R with case-based reasoning utilize variables such as carbohydrate ratio and sensitivity factor for precise insulin dosing. Hybrid and fully closed-loop systems using AI algorithms have revolutionized T1D management. These technological advances represent a paradigm shift toward personalized diabetes care with improved clinical outcomes.

DIABETES TECHNOLOGY FOR GLUCOSE MONITORING

The introduction of continuous glucose monitoring (CGM) devices is a landmark update in the field of diabetes management. These devices rely on a redox reaction catalyzed by glucose oxidase that generates an electric current proportional to the interstitial glucose levels. Most of the currently available devices provide real time glucose monitoring of the last 7-14 days. Compared to the conventional fingerstick glucose monitoring, these devices offer various advantages. One of the most significant advantages is the ability to detect the trends of blood glucose i.e. whether the glucose is rising or falling. This information can be provided to the patient and the clinician. During the period of CGM application, the user is alerted about the trend and rate of changes in glucose by appropriate symbols. Machine learning techniques like deep neural networks, gradient boosting and support vector machines are used to generate algorithms capable of predicting blood glucose thereby helping identify those with increased risk of hypoglycemia and glycemic variability. This helps plan individualized management options to improve the glycemic control and reduce the risk of hypoglycemia. Foundation models like large scale

deep learning networks trained on various health datasets are expected to enhance the predictive accuracy of these algorithms. Since CGM measure interstitial blood glucose, there is lag time of 5-10 minutes compared to the blood glucose. Hence, CGM sensor may show a normal value despite a low blood glucose. Autoregressive models have shown to predict glucose accurately over 10 minutes while long short-term memory based neural networks can do the same for at 60 minutes. Pressure at the CGM device site can lead to a phenomenon known as pressure induced sensitivity attenuation (PISA). The device interprets PISA as low blood glucose, which may lead to a false alarm and in other cases, undue suspension of the insulin pumps. This can be especially problematic if it occurs at night when the patient is asleep. Algorithms have been devised to differentiate PISA from true hypoglycemia which can potentially circumvent this issue. Various drugs like hydroxyurea, acetaminophen, vitamin C led to false positive errors depending on the technology used. Allergic dermatitis and skin infections may hinder the use of CGM in some patients. Majority of the modern CGM devices like Dexcom G6, G7, Freestyle Libre 2+ and 3+ and Guardian 4 do not require calibration by capillary glucose. However, Guardian 3 and Eversense 356 still require calibration at regular intervals.

CLINICAL EVIDENCE OF CGM

Type 1 Diabetes (T1D)

Randomized control trials and real word studies have provided sufficient justification for the use of CGM in T1D. Compared to individuals doing SMBG, those using a CGM had a mean HbA1c reduction of -0.4 to -1% and a 5-10% increase in time in range (TIR) without worsening of hypoglycemia. Studies aimed primarily at hypoglycemia reduction also showed a significant reduction of level 2 and level 3 hypoglycemia. These findings have been confirmed on real world studies and retrospective cohorts.

Type 2 Diabetes (T2D)

Type 2 diabetes too derive benefits from CGM. Individuals with T2D on intensive insulin therapy have shown a reduction of HbA1c of -0.5% to -0.8%). The rates of hypoglycemia were either unaffected or reduced across studies. Even in T2D not on insulin therapy, 6 months use of CGM led to a greater reduction of HbA1c (-0.46%) vs SMBG (-0.17%). They also had a greater time in range. CGM use not only allows customize the insulin dose, it also promotes healthy lifestyle. It increases the awareness in the user to adopt a healthy dietary pattern.

ROLE OF ARTIFICIAL INTELLIGENCE (AI) IN OPTIMIZING THERAPY

Calculation of bolus dose

The optimal insulin dose for a particular individual with diabetes depends on a number of factors. The fasting blood glucose determines the basal insulin dose. Whereas the prandial insulin doses are determined by the pre-prandial blood glucose, amount of carbohydrates consumed, glycemic index of the meal, and insulin sensitivity. Conventionally, individuals with Type 1 diabetes on MDI have been calculating these doses using the standard formula comprising of insulin sensitivity factor and correction factor along with insulin on board. However, this involves complex mathematical calculations daily. They fail to account for the physiological differences amongst individuals and are often inaccurate since they were derived based on point glucose concentrations rather than glucose trends. With the availability of continuous glucose monitoring, it is possible to collect a large amount of data regarding an individual's glycemic pattern. This data can be utilized to form decision support systems (DSS) which consider the diet, physical activity, and glucose concentrations. A DSS contains a CGM based bolus advisor which recommends the dose of insulin, a diet advisor that guides carbohydrate intake and an exercise advisor. Machine learning techniques

like linear regression, neural networks (NN) and random forests can be utilized to calculate a personalized insulin dose with data derived from CGM such as rate of change (ROC) of glucose, insulin carbohydrate ratio and sensitivity factor. One of the neural network models utilized 10 parameters in a feedforward connection in multiple layers in order to generate the output i.e., the optimal bolus

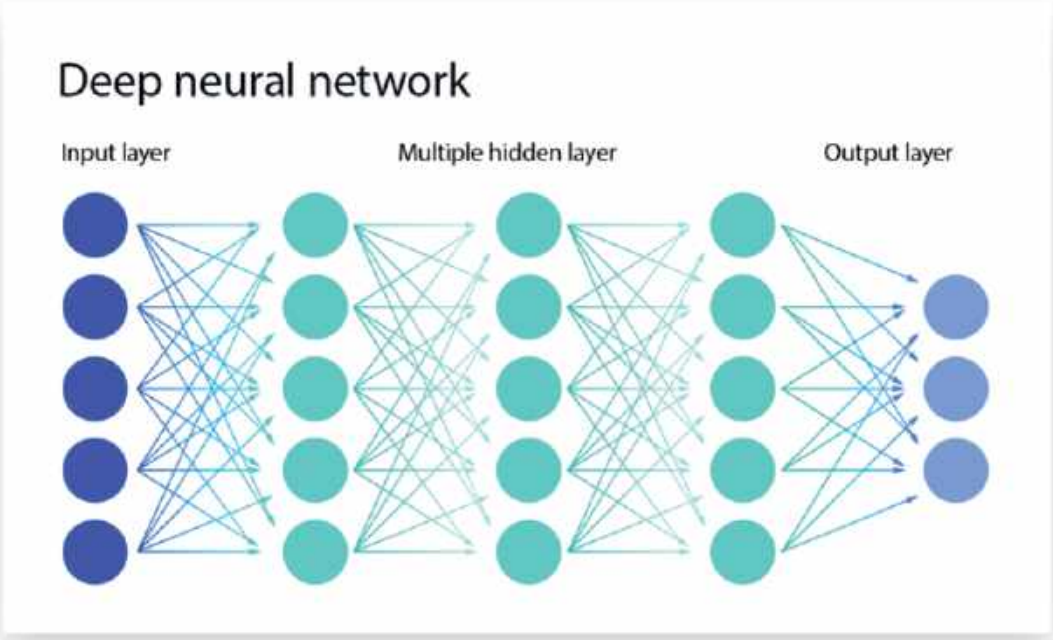

Figure 1: Ref: https://www.ibm.com/think/topics/neural-networks

dose **(Figure 1)**. The input layer comprises of 10 neurons fed with parameters related to patient's physiology (body weight and insulin sensitivity variability), the pre-prandial status (current glucose concentration, rate of change of glucose and insulin on board), therapy related parameters (insulin carbohydrate ratio, correction factor, infusion rate, target glucose and) meal carbohydrate. The algorithm combining the parameters passes through 3 hidden layers in which the fewer probable responses are filtered out. Finally, the best possible answer reaches the output layer. Simulation studies of NN revealed a better performance compared to the standard formula.

Dynamic dose modification

The physiological factors determining the insulin dose like insulin carbohydrate ratio and sensitivity factor are not fixed for a given person. They may change over time along with the changes in lifestyle necessitating periodic evaluation and modification of the dosing algorithms. Various methods have been devised to counter this issue. One such method is updating the algorithm parameters based on postprandial glucose values obtained on a run to run (R2R) fashion. In this method, the algorithm parameters are updated based on the difference between target glucose desired and glucose achieved with the previous calculation. However, this process is mechanically repetitive. For example, the patient might have hyperglycemia due to transient factors like intercurrent illness, physical or psychological stress. Ignoring such factors can lead to undue up-titration of insulin, risking an episode of hypoglycemia. To overcome this, an approach which integrates R2R with case-based reasoning (CBR) has been developed. CBR is a technique which attempts to solve a problem by studying the solutions to previous similar problems. It follows 4 sequential steps to achieve this: Retrieve – a past issue comparable to present one is brought into consideration, Reuse – the past solution is applied to the current issue; Revise – with the learnings of the past inaccuracies in achieving a result, the solution is revised to get the desired result; Retain – the current updates are saved for future reference and improvisation. This approach has been utilized in the ABC4D (Advanced Bolus calculator for Diabetes). The participants entered information about case parameters such as exercise and alcohol

and received personalized insulin bolus advice. A 6-week pilot study showed potential benefits in reducing hypoglycemia despite higher insulin doses. An open label RCT against the standard bolus calculator showed a greater reduction of HbA1c with no differences in time in range and hypoglycemia. A small study showed that deep reinforcement learning based bolus advisor has showed to improve time in range while reducing the hypoglycemia. It utilized a two-step learning framework, in which a population model is first obtained and then personalized by subject-specific data.

A study in individuals with type 2 diabetes evaluated a real-time AI-assisted insulin titration system over 12 weeks, comparing it to endocrinologist-led adjustments. It demonstrated noninferior HbA1c reductions (−1.2% vs. −1.3%) and similar hypoglycemia rates. Participants using the AI system required fewer dose adjustment visits, indicating improved efficiency in outpatient care. Patient satisfaction and adherence were also higher in the AI-assisted group.

Optimal insulin dosing in AID

With the introduction of advanced hybrid closed loop (AHCL) systems for clinical use, there has been a significant improvement in terms of glycemic control and hypoglycemia. While the AHCL depends on the user for the prandial insulin management, the complete closed loop system attempts to mimic the normal pancreatic physiology (artificial pancreas). The closed-loop automated insulin-delivery system for diabetes treatment consists of a CGM system, insulin pump, and control algorithm. The control algorithm analyzes the data received from the CGM system and automatically adjusts the insulin infusion rate. The algorithms used in closed-loop systems primarily include model predictive control, proportional-integral-derivative, fuzzy logic, and learning algorithms. Most studies involving closed loop devices are short- term ranging from few weeks to 6 months in duration. Metanalysis revealed a higher TIR, lower TBR and lower TAR compared to the standard of care. Dual hormone closed loop (DHCL) systems have been developed which are capable of delivering both insulin and glucagon attempting to mimic the physiology of pancreas. The advantage of these systems is that the user does not need to announce the meals and exercise unlike AHCL.

AI in BG management in pregnancy

Current evidence indicates that AHCL systems improve glycemic outcomes in pregnant women with Type 1 diabetes. The CRISTAL study found that pregnant individuals using the MiniMed 780G AHCL system achieved a significantly higher Time in Range (TIR) of 68.4% compared to 55.6% in the standard care group. In addition to improved metabolic control, qualitative data from the AiDAPT trial's sub-study suggests that the use of the CamAPS FX AHCL system reduces the psychosocial burden associated with diabetes management during pregnancy. Participants reported improved sleep and greater confidence in their glycemic management. The CONCEPTT trial showed that CGM use improved neonatal outcomes of large for gestational age, neonatal hypoglycemia, and NICU admissions > 24 hrs. Despite these positive outcomes, significant implementation barriers have been identified from the perspective of healthcare professionals. These include the inherent complexity of the technology, increased clinical workload, the necessity for specialized staff training, and disparities in access.

CURRENT LIMITATIONS

Most AI algorithms have been studied in adults with type 1 diabetes. Whether they will show similar benefits across the age groups is a grey area. Factors such as heart rate, sleep and stress which affect blood glucose are not incorporated in all algorithms. Long term efficacy data supporting their chronic use is lacking. Increased data sharing with connected

medical devices poses a threat to data privacy and data security.

CONCLUSION

The developments in glucose monitoring technology and evolving algorithms in machine learning hold great promise for better personalized glucose management of individuals with diabetes.

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Chapter 48

Advances in Cell Replacement Therapies in Diabetes

Arundhati Das
Shirshendu Mondal
Pranab Kumar Sahana

INTRODUCTION

Diabetes mellitus, encompassing both Type 1 (T1D) and Type 2 (T2D), is a chronic metabolic disorder characterized by insufficient insulin production or action, leading to disturbed glucose homeostasis with significant morbidity, disability and mortality. Due to rapidly growing prevalence and long-term complication including macro & microvascular changes, it has emerged as a serious public health challenge. Type1 Diabetes (T1DM) is primarily a chronic autoimmune disease causing immune mediated destructions of pancreatic islet beta cells requiring life-long insulin therapy. It has also shown a rising trend in prevalence affecting an estimated 9.5 million people globally (compared to 8.4 million in 2021, a 13 % increase) according to the recent update by International Diabetes Federation (IDF) in 2025. Despite the recent advances in newer insulin analogues and insulin delivery technologies including newer sensor augmented insulin pumps and continuous glucose monitoring tools, exogenous insulin therapy could not ensure optimum glycemic control in many of these patients owing extreme glycemic lability, recurrent episodes of severe hypoglycemia and hypoglycemic unawareness. These therapeutic challenges have fueled research into cell replacement therapies that aim to restore endogenous insulin secretion by replacing or regenerating pancreatic β-cells. This brings a paradigm shift in the management approach from treatment of diabetes to curing diabetes. The concept of beta cell replacement therapy started with whole pancreas transplantation which was first envisaged as a complementary procedure to add to the clinical success of kidney transplantation in individuals with ESRD secondary to diabetes. With the progress in transplant biology and stem cell biology, cell replacement therapies—such as islet transplantation, stem cell-derived beta cells, and biomaterial encapsulation and immunomodulation —have emerged as promising strategies to restore endogenous insulin production and potentially cure diabetes. Recent years have witnessed substantial progress in cell replacement approaches for diabetes. These advances span clinical islet transplantation, the generation and transplantation of stem cell-derived beta cells. Innovations in biomaterials, encapsulation, and immunomodulation have further enhanced the viability and safety of transplanted cells. However, significant translational challenges remain, including donor scarcity, immune rejection, safety concerns, and the need for scalable, reproducible technologies. This report synthesizes recent data-driven advances in these domains and evaluates their impact on clinical outcomes, technological development, and translational hurdles in both T1D and T2D.

Whole Pancreas Transplantation

The first simultaneous segmental pancreas-kidney transplantation was performed on a person with type 1 diabetes by Drs Kelly and Lillehei at the University

of Minnesota in 1966. This first attempt led to complete insulin independence for six days before insulin resistance (probably due to high doses of steroids) and graft pancreatitis developed. There are 3 main types of whole pancreas transplantation: simultaneous pancreas kidney (SPK), pancreas after kidney (PAK) and pancreas -alone transplant (PTA). This procedure mostly has been undertaken in individual with type1 diabetes and some cases with type 2 DM. SPK is recommended for individuals with severe diabetes and ESRD (eGFR<20 ml/min /1.73m2). PTA is recommended for patients debilitated by frequent severe, acute complications of diabetes such as ketoacidosis, hypoglycemia with or without hypoglycemic unawareness. This provided optimal glycemic control, improved the patient survival, quality of life and mitigated the risk of long-term complications by stabilizing the progression of macro-microvascular complications.

Limitation: In spite such progresses, numerous challenges still remain in this field including procurement of organ source, peri-procedural management including postoperative care or complications, engraftment issues, need of chronic immunosuppression.

Islet Transplantation

These marks yet another breakthrough in the field of beta cell replacement therapy for management of diabetes which is relatively less invasive and repeatable compared to whole pancreas transplantation and is indicated for those who are ineligible for pancreas transplantation. The modern era of islet cell transplant research was commenced by Dr Paul Lacy and his team at the Washinton University School of Medicine in the early 1960s who pioneered a major shift in this field: separation of endocrine and exocrine components of pancreas and islet purification. Further advancement occurred with the introduction of automated method for islet isolation, designed and implemented by Dr.Camillo Rocordi. Subsequently another important landmark milestone achieved with Edmonton Protocol , proposed by a team lead by James Shapiro at University of Alberta in 2000; this brought about initiation of another new era of islet cell transplant by using large number of fresh islets (>11000 islet equivalents [IEQ]/Kg) and steroid free immunosuppression regimen including on daclizumab ,sirolimus and tacrolimus , this is the first protocol succeeded in achieving 100 % one -year insulin independence rates in seven consecutive non-uremic individuals with Type1 Diabetes. The International Trial of the Edmonton Protocol for Islet Transplantation conducted in 36 individuals with T1D with severe hypoglycaemia showed that the intraportal infusion of islets from median two donor pancreases resulted in insulin independence at 1 year following the final transplantation in only 44% recipients but persistent islet graft function in insulin dependent patients still protected from severe hypoglycaemia with an improvement in overall glycaemic control. Following these findings, there were further incorporation of modifications of islet manufacturing, islet transplantation procedures, peri transplant recipient management, and immunosuppressive protocols which helped most of the recipients to achieve optimally favourable outcomes. Edmonton team followed up 255 recipients of islet transplantation prospectively for 20 years and reported that 201 (79%) got insulin independence, and 17 (70%) had sustained graft function through a median follow up of 7.4 years. Regarding the safety of Islet transplantation, the available data form Collaborative Islet Transplant Registry (CITR) and Clinical Islet Transplantation Consortium trial showed an acceptable safety profile for the high-risk subgroup of patients with T1D and recurrent severe hypoglycaemic episodes. Subsequently, Phase 3 trials of deceased donor islet transplantation have demonstrated restoration of near-normoglycemia, glycemic stability, and protection from severe hypoglycemia in immunosuppressed recipients with T1D. Thereafter,

this therapy got approval in several countries for high-risk T1D patients.

Limitations: Donor scarcity and the need for chronic immunosuppression remain major barriers

Monitoring: ^{68}Ga exendin PET imaging can be used as a potential non-invasive technique for quantification of viable islet cell mass following intrahepatic islet cell transplantation with significantly higher tracer uptake in transplanted individuals compared to controls.

INCORPORATION OF ISLET TRANSPLANTATION IN ROUTINE PRACTICE OF DIABETES CARE

Lantidra (donislecel-jujn) got U.S. FDA approval on June 2025 as the first allogeneic pancreatic islet cellular therapy made from deceased donor pancreatic cells for patients with type 1 diabetes (T1D) unable to achieve their target glycated hemoglobin (HbA1c) despite intensive insulin therapy and monitoring owing to glycemic lability, recurrent episode of severe hypoglycemia or hypoglycemic unawareness. It helps to restore glycemic control without the risk of hypoglycemia and reduce or eliminates exogenous insulin injections. Administration of Lantidra (minimum dosage: 5,000 islet equivalent/kg body weight) into the hepatic portal vein via percutaneous or transvenous transhepatic access is safer and more minimally invasive surgical procedure as compared to whole pancreas transplantation. Phase 3 clinical trial (UIH-002) showed around 2/3rd of the patients (19/30) achieved the composite efficacy endpoints (target A1c ≤6.5% and absence of severe hypoglycemic events (SHEs) through 1 year following last transplant) and 20/30 (67%) were insulin independent at 1 year post last transplant. Improvement in glycemic control was sustainable as 2/3rd of the patients assessed found to have good glycemic control after 6 years.

Today both whole pancreas and islet cell transplantation is safe and effective options of beta cell replacement therapy for people with diabetes and persistent severe hypoglycemia providing potential cure for diabetes; although whole pancreas transplantation provides higher rate and longer duration of insulin independence compared to islet cell transplantation as durability of long-term metabolic benefit directly correlates with beta cell engraftment mass.

Stem Cell-Derived Beta Cells

Transplantation of stem cell–derived beta cells has established another important landmark in field of beta cell transplantation. Differentiation of human pluripotent stem cells to pancreatic beta cells is obtained through a series of steps mimicking in vivo development. Pluripotent stem cells can be further produced from reprogrammed somatic cells called induced pluripotent stem cells (ipsc). Thus, functional beta cells capable of glucose stimulated insulin secretion can be generated in vitro from embryonic stem cells, adult stem cells (adipose tissue, bone marrow, dental pulp), somatic cells like skin fibroblasts through production of ipsc.

Technological Advances - Protocols for differentiating pluripotent stem cells (PSCs) into functional beta cells have been established, with early clinical trials showing promising result of restoration of insulin independence in immunosuppressed T1D recipient. Moreover, stem cell-derived beta cells offer an unlimited and uniform supply, addressing donor shortage issue.

Safety profile -There are risks of incomplete differentiation and teratoma formation, immune rejection. Strategies to mitigate these risks include reprogramming of somatic cells into iPSCs, selection of pure differentiated pancreatic cells, depletion of undifferentiated PSCs, and engineered suicide genes to destroy tumorigenic cells.

Clinical trials- Zimislecel is an allogeneic stem cell–derived fully differentiated islet-cell therapy. Phase 1/2 clinical trials (VX-880) of Zimislecel was started on patients with type 1 diabetes by Vertex

Pharmaceuticals in 2021, with cells transplanted intraportally into the liver under full-dose immunosuppression and has shown promising results for restoring physiologic islet cell function . By June 2024, 12 patients had been dosed; 11 of 12 showed marked reduction or complete insulin independence, and all met target HbA1c goal <7.0% and % of time in range >70% on CGM. Having this positive results, VX-880 has advanced to a phase 1/2/3 pivotal trial.

Escaping chronic immunosuppression: Concept of encapsulation of biomaterial and delivery

The aim of encapsulation of functional islet beta cells in a selectively permeable biomaterial device is to protect transplanted islets from immune response, thus mitigating the requirement for immunosuppression.

Barriers- There are technical challenges to balance immune protection with nutrient and therapeutic molecule transport (e.g., oxygen, glucose, insulin) while maintaining scalability for clinical use.

Immunomodulation: To overcome these several strategies of immunomodulation adopted including use of immunomodulatory materials, physical immune shielding, oxygen-releasing biomaterials and angiogenic growth factors to enhance vascularization and nutrient supply.

Encapsulation Devices: Various encapsulation and cellular delivery devices device for the islet and stem cell transplantation in diabetic cases evaluated in clinical trials; such as -**Encaptra device** (semipermeable pouch containing pancreatic progenitor cells), **ßAir device** (Alginate -PTFE membrane encapsulating islets), **Cell pouch device** (pre-vascularized polypropylene chambers for islet transplantation), Shielded Living **Therapeutic spheres** (cell clusters within alginate -TMID coating). These innovations are critical for sustaining long-term graft function and reducing the need for systemic immunosuppression. Several other strategies are currently in progress including engineering immune-privileged islet implantation sites, making islets immune evasive, and inducing immune tolerance in transplanted islets.

LIMITATIONS AND FUTURE DIRECTIONS

Despite these advances, several lacunae persist. Long-term graft survival, avoidance of chronic immunosuppression, and scalable manufacturing of safe, functional beta cells, cost effectiveness still remain as unresolved challenges. High-dimensional monitoring to find out determinants of sustained islet graft function and patients most likely to benefit from cell replacement therapies are emerging as critical tools for optimizing therapy. Further research is needed to modify cell differentiation protocol for producing fully functional stem cell derived beta cells and to refine encapsulation devices so that these could be incorporated into clinical practice for widespread use.

CONCLUSION

The data synthesized from recent advances in cell replacement therapies for diabetes reflects a landscape of rapid technological progress and evolving clinical strategies. Islet transplantation has set a benchmark for efficacy in high-risk T1D patients but its scalability is hampered by donor limitations and immunosuppression requirements. Stem cell-derived beta cells address these limitations, offering a renewable source of transplantable cells and demonstrating promising clinical outcomes in early trials. However, there are safety concerns, particularly the risk of teratoma formation, necessitate rigorous cell selection and engineering. Biomaterial encapsulation and delivery strategies have significantly improved the survival and function of transplanted beta cells reducing immune-mediated graft loss and enhancing vascularization.

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