

Semaglutide: Practical Prescribing Note for Physicians

CME INDIA Presentation by Dr. S. K. Gupta, Consultant Physician, Delhi.

Semaglutide Prescribing Protocol

A clinical dossier for outpatient management, dosing pathways, and sarcopenia prevention.

Optimized for the Indian Medical Context
Evidence-based guidelines (SUSTAIN, STEP, FLOW)

Protecting Muscle: The Critical Side of Semaglutide

THE HIDDEN RISK OF MUSCLE LOSS

25-40% of weight loss may be lean mass.
Without intervention, nearly half of total weight lost can be essential muscle tissue.

Sarcopenia leads to frailty and falls.
Rapid loss causes weakness, fatigue, and difficulty performing simple daily physical tasks.

High-risk groups need closer monitoring.
Elderly patients, sedentary individuals, and lean diabetics are most vulnerable to muscle wasting.

THE PREVENTION STRATEGY

Prioritize Resistance Training (3-4x/week).
Non-negotiable exercises like wall push-ups or light weights accelerated muscle catabolism.

Aim for 1.0-1.2 g/kg/day of protein.
Divide protein intake across meals to counter appetite suppression and support muscle synthesis.

Target gradual weight loss (0.5-1 kg/week).
Avoid aggressive "crash" weight loss and rapid dose escalation to protect lean mass.

Daily Supplementation for Musculoskeletal Health

- Calcium 1000-1200 mg** - Prevent bone density decline
- Vitamin D 800-2000 IU** - Support muscle function and bone health

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Rapid weight loss from Semaglutide often leads to significant lean mass depletion (sarcopenia). Clinicians must co-prescribe specific lifestyle interventions to preserve muscle and bone density.

1. Indications (Evidence-based)

| Clinical setting | Practical use |
|---------------------------------|---|
| Type 2 Diabetes Mellitus (T2DM) | Inadequate control on metformin ± other OADs |
| ASCVD / high CV risk | Proven CV benefit with semaglutide class data; subcutaneous semaglutide reduced major adverse cardiovascular events in SUSTAIN-6, and oral semaglutide also showed MACE reduction in SOUL. |
| Obesity / Overweight | BMI ≥30 kg/m ² OR BMI ≥27 kg/m ² + comorbidity; semaglutide 2.4 mg has proven weight-loss efficacy and cardiovascular benefit in eligible overweight/obesity populations. |
| Cardiorenal benefit | Reduces MACE; kidney benefit shown in FLOW in T2DM + CKD. |

- **Particularly useful in:**
 Insulin resistance
 NAFLD / MASLD
 PCOS
 Cardiometabolic risk clustering

2. Dosage & Titration (Key to tolerability)

A. Subcutaneous Semaglutide

| Situation | Usual titration |
|---|---|
| T2DM (subcutaneous) | Start 0.25 mg once weekly for 4 weeks , then 0.5 mg weekly ; if needed increase to 1 mg , then 2 mg . |
| Obesity (subcutaneous semaglutide 2.4 mg) | Escalate gradually to 2.4 mg weekly to improve tolerability. |

B. Oral Semaglutide

Important update: the older 3 mg → 7 mg → 14 mg sequence applied to the earlier oral formulation. The updated U.S. label now also includes an **R2 formulation** with a different titration schedule

| Oral semaglutide version | Practical note |
|--|--|
| Older formulation | 3 mg daily for 30 days → 7 mg → 14 mg |
| Updated R2 formulation (latest U.S. label) | 1.5 mg daily for 30 days → 4 mg for 30 days → then higher maintenance per response/tolerability. (FDA Access Data) |

👉 **Golden rule: Start low, go slow to avoid GI intolerance.** This remains clinically correct and is consistent with label-based dose-escalation logic.

The Titration Staircase



3. ⚙️ Mechanism (for clinical insight)

GLP-1 receptor agonist

↓ Appetite (central satiety)

↓ Gastric emptying

↑ Glucose-dependent insulin secretion

↓ Glucagon

This mechanism underlies both glycemic benefit and weight reduction.

4. ⚠️ Common Side Effects

| Very common / dose-dependent | Important clinical concerns |
|------------------------------|--|
| Nausea | Pancreatitis warning |
| Vomiting | Gallbladder disease / cholelithiasis / cholecystitis |
| Early satiety | Dehydration and AKI risk, especially if vomiting persists |
| Constipation / diarrhea | Worsening diabetic retinopathy can occur with rapid glucose improvement in some patients |

These adverse effects and warnings are reflected in current prescribing information and major trials.

5. Special Situations & High-Risk Groups

● Immunocompromised patients

No direct immunosuppression.

BUT: risk of reduced intake, malnutrition, and excessive weight loss in fragile patients remains a practical concern. This is more a **clinical caution** than a formal label contraindication.

Monitor:

Weight loss speed

Protein intake

Use cautiously in:

Cancer cachexia

Chronic infections such as TB / HIV when nutritional reserve is poor

● Renal disease

Generally **no dose adjustment required** in CKD, but vomiting/dehydration can precipitate AKI

● Hepatic disease

Generally safe; often useful in obesity / fatty liver settings, though not a liver-specific approved indication.

● Elderly / Frail

Start ultra-low and slow.

Avoid sarcopenia.

Ensure protein intake, mobility, and resistance activity. ADA 2026 emphasizes individualized care in older adults, with attention to nutrition, functional status, and overtreatment avoidance

● Thyroid caution

Avoid in:

Medullary thyroid carcinoma (MTC)

MEN-2 syndrome

This remains a boxed warning / contraindication in current labels.

6. Drug Interactions (Very Important in Practice)

| Interaction issue | Practical implication |
|---------------------------------|--|
| Delayed gastric emptying | May affect absorption of some oral drugs |
| Sulfonylurea / insulin | Hypoglycemia risk rises; reduce dose when needed |
| Diuretics | Dehydration risk if GI side effects occur |
| NSAIDs | AKI risk may rise in volume depletion |

- Examples commonly discussed in practice:
 - Levothyroxine
 - Antibiotics
 - Oral contraceptives

The Interaction Matrix

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Safe, but Separate Timing

- **Mechanism:** Delayed gastric emptying slows oral absorption.
- **Drugs:** Levothyroxine, Antibiotics, Oral Contraceptives.
- **Action:** Give critical drugs separately (e.g., Levothyroxine ½ hour prior).

Caution & Dose Reduction Required

- **Drugs:** Sulfonylureas (SU), Insulin.
- **Action:** High hypoglycemia risk. Proactively reduce SU/Insulin dose.
- **Drugs:** Diuretics, NSAIDs.
- **Action:** High AKI risk if volume depleted due to nausea. Monitor hydration.

Strict Avoidance / Hard Stops

- **Drugs:** DPP-4 Inhibitors (Vildagliptin, Sitagliptin, Linagliptin).
- **Action:** AVOID entirely. Same incretin pathway yields no added benefit, increases cost, and raises GI side effect risk. STOP before initiating Semaglutide.
- **Condition:** Medullary Thyroid Carcinoma (MTC) / MEN-2 syndrome.

👉 **Advice:** give critical oral drugs carefully and monitor clinical response when GI slowing is prominent. Current labels do warn that delayed gastric emptying may affect oral medication absorption.

Important correction:

“Give levothyroxine 1/2 hour before semaglutide” is **not a standard universal rule for weekly injectable semaglutide**. For **oral semaglutide**, timing instructions are formulation-specific and much more important.

7. Monitoring Protocol

Baseline

Follow-up

HbA1c

Weight: monthly

Weight, BMI

HbA1c: every 3 months

Renal function

Renal function if GI symptoms / dehydration

Liver profile

Monitor tolerability and intake

Lipid profile

Watch for persistent vomiting or abdominal pain

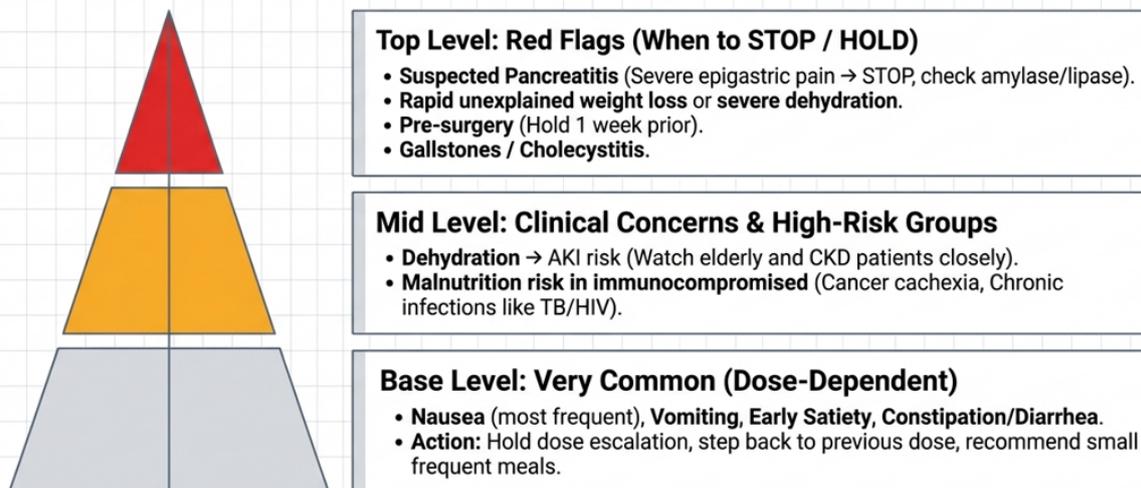
Watch for:

- Persistent vomiting
- Abdominal pain
- Visual symptoms
- Excessive weight loss
- Weakness / falls / sarcopenia signals

This is good practical OPD monitoring and is aligned with real-world use, though exact frequency should be individualized.

Side Effect Management & Escalation

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8. When to STOP / HOLD

- Suspected pancreatitis
- Severe GI intolerance
- Rapid unexplained weight loss
- Severe dehydration
- Before major surgery / procedures where delayed gastric emptying is a concern

Practical update: peri-procedural withholding recommendations have evolved over time and can vary by procedure, aspiration risk, and society guidance. A blanket “stop 1 week prior” is often used in practice for weekly dosing, but local anesthesia / endoscopy / anesthesia protocols should be checked individually.

9. Practical Pearls (Indian Context)

- High misuse risk in “cosmetic weight loss clinics”
Counsel patients:
This is **not** a lifestyle shortcut
Needs diet + exercise
Needs protein preservation
Needs follow-up
- Avoid:
BMI <25 cosmetic use without proper indication
- Watch:
Lean diabetics common in India
Risk of excessive weight loss
Risk of muscle loss
Risk of frailty in older adults

Most important to know about Semaglutide which no Pharma House tells

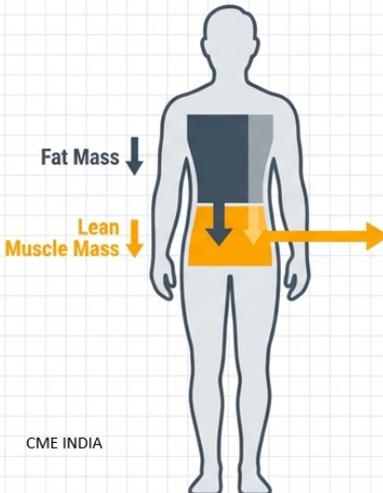
Muscle Loss (Sarcopenia) with Semaglutide – Clinical Caution

Why it happens?

Rapid weight loss = loss of both fat + lean mass
Appetite suppression → reduced protein intake
Sedentary patients → muscle catabolism

Studies of semaglutide-associated weight loss show that **lean mass does decrease**, although total body composition usually still improves because fat mass falls more. The practical concern is greatest in frail, older, sedentary, under-proteinized, or already sarcopenic patients

The Hidden Threat: Sarcopenia



Fat Mass ↓
Lean Muscle Mass ↓

25-40% of weight loss on Semaglutide can be lean muscle mass if left unprotected.

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- 1 The Mechanism of Muscle Loss**
 - Rapid weight loss removes both fat and lean mass.
 - Appetite suppression drastically reduces daily protein intake.
 - Sedentary behavior accelerates muscle catabolism.
- 2 High-Risk Vulnerability**
 - Elderly patients
 - Lean diabetics (Indian phenotype)
 - Patients with chronic illness (CKD, cancer, TB)
 - Those with low baseline protein intake
- 3 Clinical Red Flags**
 - Rapid weight loss (>2 kg/week)
 - Visible muscle wasting or fatigue
 - Difficulty rising from a chair, or falls

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Who is at HIGH RISK?

- Elderly patients
- Lean diabetics (Indian phenotype)
- Chronic illness (CKD, cancer, TB)
- Low baseline protein intake
- Sedentary lifestyle
- Frailty / poor reserve

Prevention Strategy (Must prescribe along with drug)

1. Exercise – NON-NEGOTIABLE

Resistance training is most important

3–4 times/week

Even simple:

Chair squats

Wall push-ups

Light weights

Aerobic:

Walking 30 min/day

👉 Without resistance exercise, muscle loss risk rises.

2. Protein Intake

Target usually around **1.0–1.2 g/kg/day**, and in selected obesity/weight-loss settings may need more if renal status permits.

Practical Indian advice:

Paneer

Curd

Dal

Chana

Eggs

Protein supplements if intake poor

👉 Divide protein across meals.

3. Calcium & Vitamin D

Helpful where intake is poor, deficiency is likely, or bone risk is present.

Not a semaglutide-specific rule for every patient, but very relevant in older adults and rapid weight-loss settings.

4. Weight Loss Target – Controlled, not aggressive

Ideal:

0.5–1 kg/week in many patients

Avoid:

Crash weight loss

Excess dose escalation

5. Monitoring for Sarcopenia

Clinical signs:

Weakness

Difficulty rising from chair

Fatigue

Falls

Simple OPD tools:

Hand grip strength

Mid-arm circumference

Gait speed

Red flags – Act immediately

Rapid weight loss (>2 kg/week)

Visible muscle wasting

Fatigue, falls

 Action:

Reduce dose

Increase protein

Add resistance work

Reassess treatment goal

Semaglutide: Know before you Login

1. **Expected Weight Loss – “How much, how fast, in whom?”**

Time point Practical expectation

0–4 weeks Minimal; dose-escalation phase

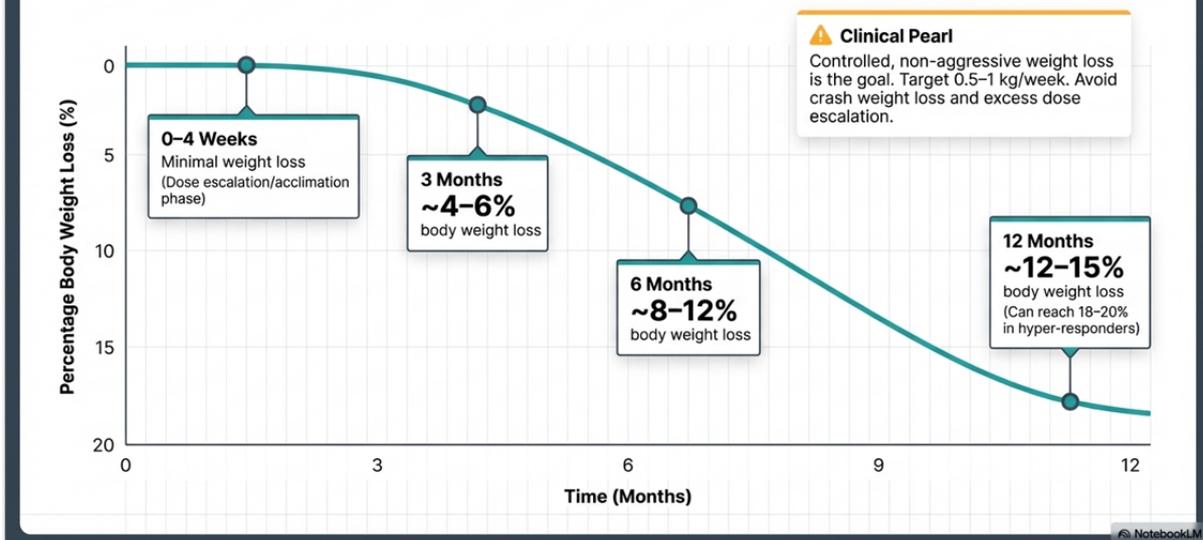
3 months ~4–6% in many responders

6 months ~8–12% in many responders

12 months ~12–15% typical in strong responders; some achieve more

These estimates are broadly consistent with STEP-era evidence and real-world expectations, but they vary by dose, adherence, baseline weight, diabetes status, and tolerability

Weight Loss Trajectory & Expectations



◆ Who responds BEST

Obese (BMI >30)
High insulin resistance
Central obesity / fatty liver
Good adherence
Adequate protein intake
No severe GI intolerance

◆ Who responds POORLY

Lean T2DM
Long-standing diabetes on insulin
Emotional eaters / binge eating
Sedentary lifestyle

👉 Clinical pearl:

If <5% weight loss at 3 months on a meaningful therapeutic dose, reassess adherence, dose, nutrition, activity, and whether this is the right drug for the right patient.

📌 2. ⚠️ Avoid combination with DPP-4 inhibitors

Vildagliptin
Sitagliptin
Linagliptin

❌ Why?

Same incretin pathway
Little added efficacy
More cost
More polypharmacy

👉 **Rule in practice:** stop DPP-4 inhibitor before starting semaglutide unless there is a very unusual reason not to. This is consistent with diabetes guideline logic.

📌 3. 🔄 Switching: Tirzepatide → Semaglutide

When to switch?

Cost issues
GI intolerance
Availability
Patient preference

Practical approach

No formal washout is usually required in routine practice; many clinicians start the next weekly agent **about 1 week after the last dose** of the prior weekly incretin, then titrate cautiously.

Important correction

Your sentence “**Semaglutide is ~10x more potent than tirzepatide**” should be **removed from academic or prescribing material** because it is **not an evidence-based clinical conversion rule**. There is **no validated dose-conversion ratio** between tirzepatide and semaglutide.

A safer practical approach is:

Start semaglutide at a conservative tolerated dose

Go slow

Expect that weight-loss efficacy may be less than tirzepatide at higher doses in many patients

This is more evidence-aligned and safer for physicians.

4. Side Effects Monitoring (Practical OPD Protocol)

👁️ A. Eye Monitoring (Retinopathy risk)

Why?

Rapid HbA1c fall may transiently worsen diabetic retinopathy in susceptible patients. This signal was noted in SUSTAIN-6 and is also reflected in current labelling.

Who is high-risk?

Pre-existing diabetic retinopathy
Very high HbA1c
Rapid glucose drop

What to do?

| |
|---|
| Baseline fundus exam in at-risk patients Repeat at 3–6 months if high-risk |
|  Red flags: Blurring of vision Floaters Visual change |
|  B. Weight Monitoring |
| Weekly self-monitoring Monthly clinic review |
|  Concern if: 1.5–2 kg/week loss Weakness Sarcopenia features |
|  C. Sugar Monitoring |
| SMBG initially when clinically needed HbA1c every 3 months |
|  Watch for: Hypoglycemia if on insulin / SU Excessively rapid glycemc drop |
|  D. Dehydration & Renal Monitoring |
| Check creatinine if: Persistent vomiting Elderly CKD Poor intake |

The OPD Dashboard

| | |
|---|--|
|  Eye Monitoring |  Weight & Muscle Monitoring |
| Risk: Rapid HbA1c fall worsens pre-existing retinopathy. Protocol: Baseline fundus exam ; repeat at 3–6 months . Action: If blurring or floaters occur, refer to ophthalmology and slow glycemc reduction. | Protocol: Weekly self-monitoring ; monthly clinic checks . Evaluate hand grip strength , mid-arm circumference , or gait speed . Action: If loss exceeds 1.5–2 kg/week or weakness occurs, reduce dose and ensure protein intake . |
|  Glycemic Monitoring |  Renal & Hepatic Monitoring |
| Protocol: SMBG initially 2-3x/week ; HbA1c every 3 months . Action: Watch for excessive drop (>2% HbA1c in 3 months) or hypoglycemia . Reduce SU/Insulin early . | Protocol: Baseline KFT, LFT, Lipid profile . Action: Check creatinine immediately if patient presents with persistent vomiting , especially in the elderly (AKI risk). Safe for Hepatic/NAFLD patients . |

5. When Side Effects Occur – What to Do

GI intolerance

Hold dose escalation
Step back to previous dose
Small frequent meals

Persistent vomiting

Stop drug temporarily
Hydrate
Check renal function

Suspected pancreatitis

Severe epigastric pain → STOP immediately
Check amylase / lipase
Evaluate urgently

Final Clinical Takeaways

- ✓ Expect meaningful weight loss in the right patient, but not every patient loses equally
- ✓ Avoid DPP-4 inhibitors alongside semaglutide
- ✓ Switching from tirzepatide to semaglutide should be cautious; there is **no validated fixed**

conversion ratio

- ✓ Monitor:

 Eye

 Weight

 Sugar

 Renal function

 Muscle preservation

- ✓ Always co-prescribe:

Exercise

Protein

Monitoring

Counseling

- ! Otherwise risk rises for:

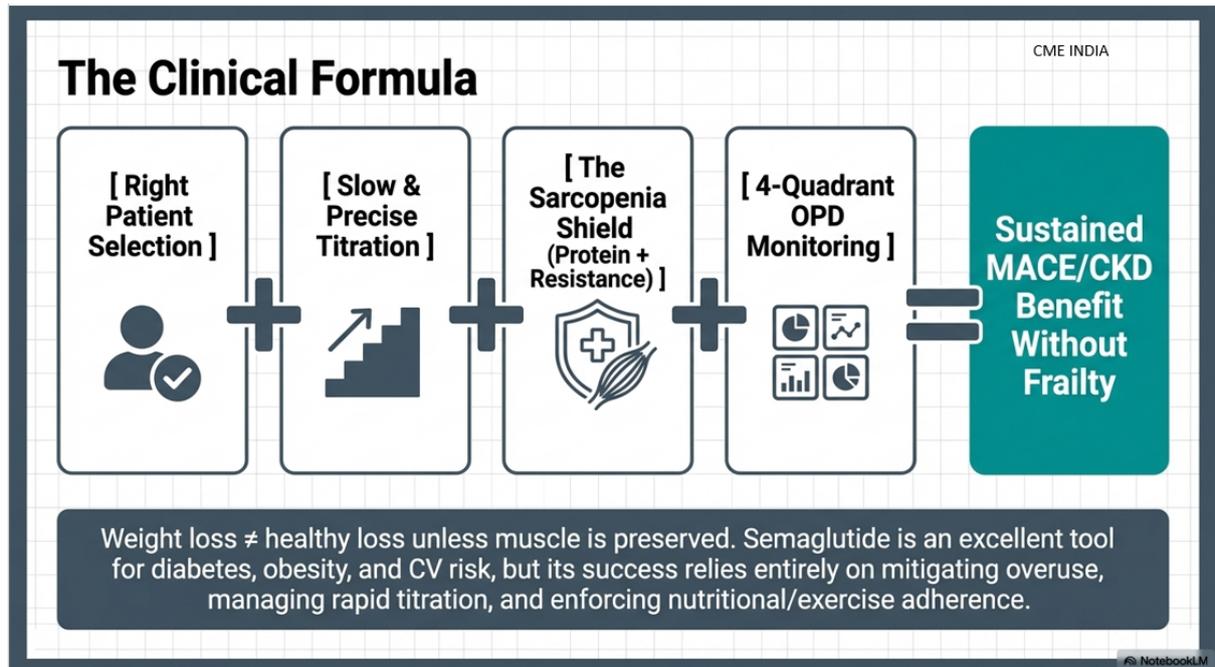
Sarcopenia

Frailty

Falls

Discontinuation

Poor long-term outcomes



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