SEMAGLUTIDE

GLP-1 Receptor Agonist | Ozempic / Wegovy / Rybelsus

FDA-Approved: T2D (2017) | Obesity (2021) | Oral T2D (2019) | CV Risk Reduction | CKD | MASH

1. Peptide Description

- **Brand names:** Ozempic (SC, T2D); Wegovy (SC, obesity/CV risk/MASH); Rybelsus (oral, T2D)
- **Classification:** GLP-1 receptor agonist (GLP-1 RA) — incretin mimetic; once-weekly SC or once-daily oral
- **Structure:** Synthetic 31-amino acid peptide; 94% homology to native GLP-1(7-36) amide; MW 4113.58 g/mol
- **Key structural modifications:** (1) Aib8 substitution — confers DPP-4 resistance; (2) Arg34 / C18 fatty diacid (dicarboxylic acid) at Lys26 via linker — enables >99% albumin binding, extending half-life to ~168 hours
- **Half-life:** ~168 hours (~7 days) SC — enables once-weekly dosing; steady state reached at 4–5 weeks
- **Bioavailability:** ~89% SC; ~0.4–1% oral (Rybelsus) — SNAC absorption enhancer overcomes GI peptide degradation barrier
- **Metabolism / elimination:** Proteolytic cleavage and beta-oxidation; no active metabolites of concern; eliminated primarily via feces, urine (3%); no dose adjustment for renal or moderate hepatic impairment
- **FDA approvals:** Ozempic (T2D, 2017); Rybelsus oral (T2D, 2019); Wegovy (obesity, 2021); CV risk reduction, CKD, and MASH indications added via label expansions 2023–2024
- **Landmark distinction:** First anti-obesity drug to demonstrate cardiovascular event reduction (SELECT trial, non-diabetic population)

⚠ **BLACK BOX WARNING:** *Thyroid C-cell tumors observed in rodent studies. Contraindicated in personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2). Human relevance not established.*

2. Modes of Action & Mechanisms

GLP-1R activation — glucose-dependent insulin secretion and beta-cell effects

- Binds GLP-1 receptor (Class B GPCR, Gs-coupled) on pancreatic beta-cells with 94% GLP-1 homology → adenylyl cyclase activation → cAMP elevation
- cAMP/PKA pathway: phosphorylates CREB → activates beta-cell gene transcription → proinsulin synthesis → insulin granule loading
- cAMP/Epac2 pathway: Epac2 activation → Rap1 → intracellular Ca^{2+} surge → insulin granule exocytosis — the physical release mechanism
- PI3K/Akt pathway: beta-cell survival, proliferation, and apoptosis resistance — long-term preservation of beta-cell mass
- **Glucose-dependent only:** all insulin release requires the presence of glucose — the intrinsic mechanism that prevents hypoglycemia, unlike sulfonylureas

Alpha-cell suppression, gastric slowing, and central satiety

- Suppresses alpha-cell glucagon release in a glucose-dependent manner → reduces hepatic gluconeogenesis and fasting glucose output
- Counter-regulatory glucagon response to hypoglycemia is preserved — the liver can still mount emergency gluconeogenesis when genuinely needed
- Delays gastric emptying → prolongs nutrient absorption → blunts postprandial glucose excursions and extends postprandial satiety
- Crosses the blood-brain barrier → activates GLP-1Rs in the hypothalamic arcuate nucleus, POMC/CART neurons → reduces hunger signaling, increases satiety — the primary weight loss mechanism

Cardiovascular and renal mechanisms

- Direct GLP-1Rs on cardiomyocytes and endothelium → anti-inflammatory and anti-atherogenic effects
- NF-κB suppression → reduced pro-inflammatory cytokines (TNF-α, IL-6, CRP) — confirmed in SELECT trial; CRP reduced ~38%
- Nrf2/HO-1 pathway activation → antioxidant defense (preclinical)
- Renal: natriuresis, RAAS modulation, reduced oxidative stress, anti-fibrotic actions in kidney — multiple convergent mechanisms behind FLOW trial outcomes

Pleiotropic molecular pathways

- **AMPK modulation:** Semaglutide-induced weight loss and fat cell lipolysis activate AMPK in peripheral tissues — improves metabolic homeostasis, suppresses mTOR, enhances autophagy and mitophagy
- **NF-κB suppression + Nrf2 activation:** Anti-inflammatory (NF-κB → IL-1β, TNF-α, IL-6 ↓) plus antioxidant defense (Nrf2 → HO-1, glutathione peroxidase, SOD ↑) — confirmed in clinical trials and preclinical models
- **AMPK/mTOR balance:** AMPK activation counteracts mTOR overactivation seen in obesity and NAFLD; improved balance drives autophagy, reduces hepatic fibrosis, improves insulin sensitivity
- **SIRT1 activation:** Improved mitochondrial efficiency and redox balance — preclinical data; mechanistic basis for renal and hepatic protection
- **Macrophage polarization:** NF-κB inhibition + AMPK + Nrf2 activation drive M1 (pro-inflammatory) → M2 (anti-inflammatory) macrophage shift — preclinical; relevant to atherosclerosis and liver disease

NOTE: *The AMPK/mTOR/NF-κB/Nrf2 axis is shared across GLP-1 RAs but is most robustly validated for semaglutide through multiple large RCTs. These pathways mechanistically link all of semaglutide's multi-organ benefits — cardiovascular, renal, hepatic, and emerging neuroprotective — in a unified cellular efficiency framework.*

3. Main Points of Clinical Relevance

1 SELECT trial — first anti-obesity drug to show CV mortality benefit in non-diabetics

SELECT (n=17,604, BMI ≥27, established CVD, no diabetes, median 3.3 years, 2.4 mg weekly): 20% MACE reduction (HR 0.80, p<0.001); nonfatal MI −28% (HR 0.72); all-cause death −19% (HR 0.81); heart failure composite −18% (HR 0.82). CRP reduced ~38% — confirming the anti-inflammatory mechanism. Critically, CV benefit was independent of HbA1c change — this is not a glucose effect. This trial established semaglutide as a cardiovascular drug, not merely a weight loss or diabetes drug, and represents a paradigm shift in how obesity is treated.

2 SUSTAIN-6 — 26% MACE reduction in T2D, with a retinopathy signal to monitor

SUSTAIN-6 (n=3,297, T2D, 2 years): 26% MACE reduction (HR 0.74); 39% reduction in nonfatal stroke (HR 0.61); nephropathy reduced 36% (HR 0.64). One important signal: diabetic retinopathy

complications were increased (HR 1.76, p=0.02). This is thought to reflect rapid initial glucose lowering in patients with pre-existing, poorly-controlled retinopathy — similar to what is seen with intensive insulin therapy. This is not a reason to avoid semaglutide, but it mandates baseline retinal exam and 6-monthly follow-up in T2D patients with existing retinopathy.

3 STEP program — ~15% weight loss approaching bariatric surgery outcomes

STEP 1 (n=1,961, BMI ≥30, no T2D): −14.9% weight loss vs −2.4% placebo; 84.6% achieved ≥5% loss; 50.5% achieved ≥15% loss. STEP 2 (T2D): −9.6% weight loss; HbA1c −1.6%. STEP 3 (with intensive behavioral therapy): −16.0%. STEP 4 (maintenance): −17.4% maintained in those who continued. STEP-HFpEF: −13.3% in obese heart failure patients with improved symptoms and exercise function. Head-to-head vs. liraglutide: 50.5% achieved ≥15% loss on semaglutide vs. 14.4% on liraglutide — a clinically meaningful separation. Weight loss plateaus at ~60–68 weeks; set expectations accordingly.

4 FLOW trial — 24% reduction in kidney disease progression in T2D + CKD

FLOW (T2D + chronic kidney disease): 24% reduction in kidney risk progression (eGFR decline, dialysis, transplant, renal death). This established semaglutide as the fourth pillar of diabetic kidney disease management — alongside RAAS inhibitors, SGLT2 inhibitors, and finerenone. No dose adjustment is required for renal impairment, and the renal benefit is mediated through multiple convergent mechanisms: improved glycemia, blood pressure reduction, weight loss, RAAS modulation, reduced renal oxidative stress, and direct anti-fibrotic effects via SIRT1/Nrf2 pathways.

5 NASH/MASH resolution — 59% resolution rate in Phase 2 trial

Phase 2 NASH trial (semaglutide 0.4 mg SC daily): 59% NASH resolution vs. 17% placebo — one of the highest resolution rates ever demonstrated in this indication. Wegovy now carries an approved indication for metabolic dysfunction-associated steatohepatitis (MASH). Mechanism: AMPK/mTOR rebalancing reduces hepatic lipid accumulation and fibrosis; NF-κB suppression decreases hepatic inflammation; improved insulin sensitivity reduces de novo lipogenesis. This is a genuine structural liver benefit, not merely weight-related fat reduction.

6 Discontinuation leads to weight regain — treatment is long-term or indefinite

STEP 1 extension: approximately two-thirds of lost weight was regained within one year of stopping semaglutide. This is not a drug failure — it reflects the chronic disease nature of obesity. STEP 4 data supports indefinite treatment. The clinical strategy: achieve goals on full-dose semaglutide, then titrate to the lowest effective maintenance dose — not discontinue. Concurrent lifestyle intervention (nutrition quality, resistance training, Zone 2 cardio, sleep optimization) is non-negotiable if the aim is durable benefit. Microdosing — titrating to the lowest dose that maintains weight and retains the pleiotropic pathway benefits — is a clinically rational approach to long-term management.

7 Slow titration eliminates most GI side effects — the titration is the intervention

Nausea (40–44%), diarrhea (25–30%), vomiting (20–24%) are predominantly dose-escalation phenomena that peak at weeks 8–12 and then attenuate. 98.1% of GI adverse events are mild-to-moderate and non-serious. The standard escalation schedule (doubling dose every 4 weeks) is too aggressive for many patients. The educator's approach: advance only when the current dose is fully tolerated; hold for 2–4 weeks if symptomatic; consider intermediate doses (0.75 mg as a bridge between 0.5 and 1.0 mg). Target weight loss of 0.5–0.75 lbs/week — the sweet spot that preserves lean mass, avoids aesthetic concerns, and minimizes adverse events. Hydration counseling is essential — dehydration from GI effects can precipitate acute kidney injury.

4. Dosing Instructions & Delivery Options

Ozempic — Type 2 Diabetes (SC)

Phase	Dose	Duration	Notes
Initiation	0.25 mg SC weekly	4 weeks	Not therapeutic for glycemic control — GI adaptation only

Phase	Dose	Duration	Notes
First therapeutic	0.5 mg SC weekly	4+ weeks	Assess tolerability; do not advance if symptomatic
Escalation	1.0 mg SC weekly	4+ weeks	Standard maximum for most T2D patients
Higher dose	2.0 mg SC weekly	Ongoing	Newer label option for additional glycemic control

Wegovy — Weight Management / Obesity / CV Risk (SC)

Label Schedule	Educator's Preferred Pace	Dose	Notes
Week 1–4	Weeks 1–4	0.25 mg SC weekly	GI adaptation; not weight-therapeutic yet
Week 5–8	Weeks 5–8	0.5 mg SC weekly	Advance only if 0.25 mg fully tolerated
Week 9–12	Weeks 9–16	1.0 mg SC weekly	Hold longer if any GI symptoms; bridge dose available
Week 13–16	Weeks 17–24	1.7 mg SC weekly	Reassess tolerability before final escalation
Week 17+	Week 25+	2.4 mg SC weekly	Target maintenance dose; evaluate at week 16 of full dose
16-wk assessment	16-wk assessment	Review response	Discontinue if <5% weight loss at 2.4 mg after 16 weeks

Rybelsus — Oral Semaglutide (T2D)

Phase	Dose	Duration	Notes
Month 1	3 mg PO daily	4 weeks	Initiation; take 30 min before first food/drink with ≤4 oz plain water only
Month 2	7 mg PO daily	4 weeks	First therapeutic oral dose
Month 3+	14 mg PO daily	Ongoing	Maximum oral dose; titrate slowly — oral nausea is harder to manage than SC

Key dosing principles: Go slow — slower than the label, slower than you think is necessary. Nausea peaks weeks 8–12; if the patient is symptomatic, hold the current dose for an additional 2–4 weeks rather than advancing. Target 0.5–0.75 lbs/week weight loss — not faster. Rybelsus is the most difficult to titrate: oral GI exposure makes nausea more pronounced; strict administration rules (30 min fasted, water only) are non-negotiable for adequate absorption. If switching from another GLP-1 RA, start semaglutide the day after the last dose of the prior agent. Same injection day each week; rotate sites. Obtain baseline eye exam and repeat annually — especially in T2D patients with pre-existing retinopathy.

5. Evidence Profile

Evidence tier legend: ● *Human RCT / clinical trial* ○ *Animal / preclinical* ◎ *Structural / mechanistic* ✕ *Critical gap* ~ *Theoretical / emerging*

- ● SELECT (n=17,604): 20% MACE reduction in non-diabetic obese patients with established CVD — first anti-obesity CV outcome trial (Lincoff 2023)*Human RCT*
- ● SELECT: CV benefit independent of HbA1c change; CRP reduced ~38%; all-cause death −19% (Lincoff 2024)*Human RCT*
- ● SELECT: HF composite reduced 18% (HR 0.82) — expanding into heart failure with obesity*Human RCT*
- ● SUSTAIN-6 (n=3,297, T2D): 26% MACE reduction, 39% nonfatal stroke reduction, 36% nephropathy reduction; retinopathy signal (HR 1.76) (Marso 2016)*Human RCT*
- ● STEP 1 (n=1,961): −14.9% weight loss vs −2.4% placebo; 84.6% ≥5% loss; 50.5% ≥15% loss (Wilding 2021)*Human RCT*
- ● STEP 2 (T2D): −9.6% weight loss; HbA1c −1.6% at 2.4 mg*Human RCT*
- ● STEP 3 (+ intensive behavioral therapy): −16.0% weight loss — synergy with lifestyle intervention*Human RCT*
- ● STEP 4 (maintenance): −17.4% sustained; ~2/3 weight regained within 1 year of discontinuation (Rubino 2021; Wilding 2022)*Human RCT*
- ● STEP-HFpEF (n=529): −13.3% weight loss in HFpEF + obesity; improved symptoms, exercise capacity, NT-proBNP (Kosiborod 2023)*Human RCT*
- ● STEP TEENS: −16.1% BMI reduction in pediatric patients age 12+ (Wegovy approved)*Human RCT*
- ● FLOW (T2D + CKD): 24% reduction in kidney disease progression; no dose adjustment needed for renal impairment (Perkovic 2024)*Human RCT*
- ● NASH Phase 2 (semaglutide 0.4 mg SC daily): 59% NASH resolution vs 17% placebo; MASH indication added to Wegovy label (Newsome 2021)*Human RCT*
- ● SUSTAIN program: HbA1c reduction 1.0–1.8% across T2D trials; confirmed glycemic superiority vs. other GLP-1 RAs*Human RCT*
- ○ NF-κB suppression, Nrf2/HO-1 activation, macrophage M1→M2 polarization — mechanistic basis for CV and renal benefit (preclinical)*Animal / mechanistic*
- ○ AMPK/mTOR rebalancing → improved autophagy, hepatic lipid reduction, anti-fibrotic renal effects (preclinical)*Animal / mechanistic*
- ○ SIRT1 upregulation — mitochondrial efficiency and renal oxidative stress reduction (preclinical)*Animal / mechanistic*
- ~ Neuroprotection: GLP-1R in brain; Alzheimer's and Parkinson's trials ongoing; mild cognitive impairment data emerging*Early clinical / preclinical*
- ~ Cancer incidence reduction: retrospective signals for obesity-associated cancers (colon, breast, prostate, lung) — mechanistic rationale; not RCT-confirmed*Emerging / theoretical*
- ✕ Long-term cancer risk with chronic GH/IGF-1 or GLP-1 exposure (>5 years) — not established*Critical gap*
- ✕ Head-to-head vs. tirzepatide for cardiovascular outcomes — not yet completed*Critical gap*
- ✕ Optimal maintenance microdosing strategy after goal achievement — not studied*Critical gap*
- ✕ Neuroprotective efficacy in humans — Phase 3 trials not yet completed*Critical gap*

Comparative efficacy: GLP-1 RA class

Agent	Frequency	Weight Loss	MACE Reduction	CKD Data	HbA1c Reduction
Semaglutide SC	Weekly	−14.9% (STEP 1)	−20% SELECT; −26% SUSTAIN-6	−24% FLOW	1.0–1.8%
Semaglutide oral	Daily	−7–11%	Under investigation	Under investigation	Similar SC

Agent	Frequency	Weight Loss	MACE Reduction	CKD Data	HbA1c Reduction
Liraglutide	Daily	−5–8%	−13% LEADER	−22% composite	1.0–1.5%
Tirzepatide	Weekly	−15–22.5%	SURPASS-CVOT pending	Under investigation	2.0–2.4%
Dulaglutide	Weekly	−3–5%	−12% REWIND	eGFR decline slowed	~1.0%
Exenatide ER	Weekly	−2–4%	Neutral (EXSCEL)	Limited	~0.9%

6. Clinical Considerations

Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC) — absolute contraindication (black box)
- Multiple Endocrine Neoplasia type 2 (MEN2) — absolute contraindication (black box)
- Known serious hypersensitivity to semaglutide or any excipient
- Pregnancy — contraindicated; discontinue at least 2 months before planned conception
- History of pancreatitis — use with caution; assess risk-benefit individually; monitor amylase/lipase
- Do not combine with other GLP-1 RAs or DPP-4 inhibitors — additive class effects without additive benefit; increased GI risk

Patient selection

- **T2D:** HbA1c inadequately controlled; BMI ≥27; especially with established CVD (SUSTAIN criteria) or CKD stages 3–4 (FLOW criteria)
- **Obesity / CV risk:** BMI ≥30, or BMI ≥27 with established ASCVD and no diabetes (SELECT criteria) — first-line choice
- **MASH:** Wegovy now indicated; consider in obese patients with confirmed NASH/MASH on imaging or biopsy
- **HFpEF + obesity:** STEP-HFpEF data supports semaglutide for symptom improvement and functional benefit
- **Pediatric obesity:** Wegovy approved age 12+ with BMI ≥95th percentile; STEP TEENS data supports use
- **Do not select if:** MTC/MEN2 history; active pancreatitis; pregnancy planned within 2 months; active cancer (use caution)

Monitoring protocol

Timepoint	Labs / Assessments	Clinical Focus
Baseline	HbA1c, fasting glucose, fasting insulin, CMP, CBC, lipid panel (triglycerides), thyroid function, calcitonin (if indicated), serum lipase/amylase, eGFR/UACR, liver panel; body weight, BMI, waist circumference; retinal exam (T2D); DEXA or InBody	Exclude contraindications; establish full metabolic and end-organ baseline
Week 4–8	Fasting glucose, body weight, GI symptom assessment, BP, heart rate; HbA1c if diabetic	Tolerability check; dose escalation decision; early glucose signal

Timepoint	Labs / Assessments	Clinical Focus
Month 3	HbA1c, fasting glucose, CMP, body weight, waist circumference; lipid panel (triglycerides 3–4 months to respond)	Glycemic and lipid response; intermediate tolerability review
Month 6	Full metabolic panel, IGF-1 (if co-using secretagogues), eGFR/UACR, liver panel, body composition (DEXA or InBody)	Renal and hepatic monitoring; body composition intermediate assessment
Month 12+	Full lab panel + retinal exam + cardiac assessment if indicated + calcitonin if MTC concern + mental health screen	Annual comprehensive safety and efficacy review
Every visit	Body weight, BMI, waist circumference, BP, heart rate, GI symptom review, hydration assessment	Ongoing safety, dose appropriateness, weight loss rate (target 0.5–0.75 lbs/week)

Monitor for retinopathy every 6 months in T2D patients with pre-existing retinopathy (SUSTAIN-6 signal). Monitor amylase/lipase and obtain imaging promptly if abdominal pain is severe or persistent — pancreatitis is rare (<1%) but requires immediate discontinuation. Weight regain monitoring after dose reduction is essential.

Drug interactions & practical cautions

Interaction / Caution	Detail
Insulin	Reduce basal insulin by 10–20% at semaglutide initiation to avoid hypoglycemia; titrate based on glucose monitoring
Sulfonylureas	Reduce dose or discontinue when adding semaglutide — significant hypoglycemia risk with combination; glucose-dependent mechanism does not eliminate sulfonylurea risk
SGLT2 inhibitors	Complementary and additive: CV, renal, and weight benefits via different mechanisms; preferred combination for CKM syndrome and four-pillar DKD therapy; monitor for dehydration/UTI
Metformin	Additive glycemic benefit; AMPK activation is complementary; use with caution — potential hypoglycemia in some settings; consider impact on muscle mass and B12 depletion with long-term metformin
Finerenone	Four-pillar DKD combination (RAAS inhibitor + SGLT2i + finerenone + semaglutide); emerging evidence; monitor potassium, renal function
Oral medications (narrow TI)	Delayed gastric emptying may reduce absorption of narrow therapeutic index drugs (warfarin, levothyroxine, certain antibiotics); administer these ≥1 hour before semaglutide injection
Other GLP-1 RAs / DPP-4 inhibitors	Do not combine — increased class side effects without synergistic benefit; DPP-4 inhibitors can be discontinued when starting GLP-1 RA
Dehydration / AKI risk	GI side effects cause fluid loss; actively counsel patients on hydration; monitor eGFR if vomiting/diarrhea is prolonged — acute kidney injury risk
Retinopathy (T2D)	Rapid initial glucose normalization may transiently worsen diabetic retinopathy in poorly-controlled patients — baseline exam required; 6-monthly follow-up during first year in at-risk patients
Injection technique	SC abdomen, thigh, or upper arm; rotate sites weekly; same day each week; room temperature before injection; do not mix with insulin

Multi-specialty clinical positioning

Specialty	Primary Indication	Key Evidence
Cardiometabolic / CV	Obesity + established ASCVD (no diabetes); HFpEF + obesity	SELECT (20% MACE); STEP-HFpEF (symptom improvement)
Endocrinology / T2D	T2D inadequately controlled; second-line or first-line vs. metformin	SUSTAIN-6 (26% MACE); HbA1c −1.0–1.8%; weight loss
Nephrology	T2D + CKD stages 3–4; four-pillar DKD therapy	FLOW (24% kidney risk reduction); no dose adjustment needed
Hepatology	NASH/MASH + obesity	59% NASH resolution Phase 2; MASH label indication
Primary care / obesity	BMI ≥30 (or ≥27 + comorbidity); weight management	STEP 1 (−14.9%); 50.5% achieving ≥15% loss
Neurology (emerging)	Neuroprotective / Alzheimer's / Parkinson's	GLP-1R in brain; Phase 2 trials ongoing; not yet standard

Clinical bottom line: Semaglutide is the most comprehensively validated GLP-1 RA and the most evidence-rich peptide in this series. SELECT made it the first anti-obesity drug to prove CV mortality benefit in non-diabetic patients. FLOW established it as a kidney-protective agent. STEP proved ~15% weight loss approaching bariatric outcomes. NASH Phase 2 gave it a liver indication. The mechanisms are clear — AMPK/mTOR/NF-κB/Nrf2/SIRT1 — and the clinical breadth is unmatched. The clinical discipline is straightforward: slow the titration to match patient tolerance, target 0.5–0.75 lbs/week weight loss, baseline and annual eye exams, active hydration counseling, and plan for long-term treatment — not a finite course. Discontinuation without lifestyle foundation leads to two-thirds weight regain within a year. Use it as the cardiometabolic cornerstone, combine with SGLT2 inhibitors for CKM syndrome, and consider semaglutide as the metabolic foundation before layering any GH secretagogue or anabolic peptide strategy.

Final Note: Where Semaglutide stands in the GLP-1 RA class and the broader peptide landscape

Semaglutide is the current standard-bearer of the GLP-1 RA class — not because liraglutide failed, but because semaglutide built on liraglutide's foundation and extended it further in every direction: greater weight loss, broader FDA indications, more cardiovascular outcomes data, renal protection confirmed in CKD, and a liver indication. Tirzepatide (GLP-1 + GIP dual agonism) achieves greater weight loss (15–22%) but its CV outcomes data is still pending; semaglutide holds the most complete evidence-based profile of any agent in the class as of 2026.

Vs. liraglutide: semaglutide wins on weight loss magnitude (~15% vs ~8%), dosing convenience (once-weekly vs. once-daily), HbA1c reduction, and breadth of indications. Liraglutide retains a role in patients who need once-daily dosing for titration precision or cost/insurance considerations. The shift from daily to weekly injection is not trivial — adherence improves substantially.

In the context of the broader peptide series: semaglutide and the GLP-1 RAs are the metabolic foundation layer. Optimizing insulin sensitivity, reducing visceral adiposity, activating AMPK, and restoring mitochondrial efficiency through GLP-1 RA therapy creates the cellular environment where GH secretagogues (ipamorelin, GHRP-2, MK-677), anabolic agents, and other peptide strategies can operate most effectively. The sequencing principle: metabolic optimization first, anabolic support second — and semaglutide is the most powerful metabolic optimizer in this series.