M5.1 — Knowledge Check (CME)

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Lesson: M5.1 Obesity Pathophysiology — Hormonal, Metabolic & Neural Drivers **Format:** 15 case-based questions. Each has a rationale + reference. **Passing threshold:** 12/15 (80%) for CME credit. **Estimated time:** 25–30 minutes.

How to use this

This assessment tests retention of the clinical positions in M5.1. It is not a memory test of trial numbers; it's a judgment test about *how* the evidence informs decisions. Read the question, pick the best answer, then read the rationale even if you got it right — the rationale often surfaces the nuance the question can't.

Section A — Pathophysiology & framing (questions 1–4)

Question 1

A 42-year-old patient with a 15-year history of dieting and 50 lb of weight loss-and-regain cycles asks why diets stop working. Which best describes the principal mechanism?

A. Patients become less disciplined over time and "give up" on calorie restriction. B. Resting metabolic rate drops, hunger hormones (ghrelin) rise, satiety hormones (leptin, PYY) fall, and thyroid signaling shifts — these adaptations persist for years and are not extinguishable by willpower. C. The thyroid gland becomes permanently damaged from repeated dieting cycles. D. The body's set point gradually rises with each diet cycle, so the same effort produces less weight loss.

Correct: B

Rationale: Sumithran 2011 (PMID 22029981) demonstrated that ghrelin, PYY, leptin, GIP, CCK, insulin, and amylin remain altered in the appetite-stimulating direction at 62 weeks after a 10% weight loss. Rosenbaum 2008 (PMID 18842775) and Fothergill 2016 (PMID 27136388, the Biggest Loser cohort) show persistent metabolic adaptation of ~300–500 kcal/day at multi-year time scales. This is the central biological insight that reframes obesity from a willpower problem to a defended physiologic state.

Option A is the cultural narrative the lesson explicitly rejects. C is incorrect — there is no evidence of permanent thyroid damage. D conflates set-point ratcheting (which happens with sustained caloric excess, not with dieting) with the adaptive response.

Question 2

Which best describes the relationship between leptin and obesity in established disease?

A. Patients with obesity have low circulating leptin, which is why they don't feel full. B. Patients with obesity have high circulating leptin, but the hypothalamus has become resistant to the signal — analogous to insulin resistance. C. Leptin is suppressed during caloric restriction and rebounds after weight regain. D. Leptin acts primarily on adipose tissue, not the brain.

Correct: B

Rationale: In established obesity, leptin is typically elevated, sometimes markedly so, but the hypothalamic response is blunted ("leptin resistance"). The signal is present; the receiver is unresponsive. This is mechanistically analogous to insulin resistance. The patient's experience is hunger and reduced satiety even when fat stores are excessive — not because they're "greedy" but because the satiety signal isn't being received.

A is the opposite of the truth. C is partially correct (leptin does fall during caloric restriction) but misses the established-disease picture. D is incorrect — adipocytes *produce* leptin; it acts on the hypothalamus.

Question 3

A patient asks why "eat less, move more" failed for them across 15 years of dieting. Which response best reflects current obesity-medicine framing?

A. "You probably need a stricter diet plan." B. "Your effort wasn't the problem. After even modest weight loss, the body defends the higher weight with hormonal and metabolic changes that persist for years. The intervention has to address the biology, not just the behavior." C. "Your willpower may need to be supported with a coach or accountability partner." D. "Genetics is destiny — there's not much we can do."

Correct: B

Rationale: This is the "biology, not blame" reframe at the center of M5.1. It is supported by Leibel 1995, Rosenbaum 2008, Sumithran 2011, and Fothergill 2016. Option A doubles down on the failed paradigm. C misattributes the problem to motivation. D is fatalistic and ignores the pharmacologic toolkit that genuinely intervenes in the biology. The honest, evidence-based answer is B.

Question 4

The Diabetes Prevention Program (DPP) and Look AHEAD trials are landmark studies of intensive lifestyle intervention. The most accurate summary of their long-term weight-management findings is:

A. Lifestyle alone produces durable 15–20% weight loss in most patients. B. Lifestyle intervention is effective for diabetes prevention but produces modest sustained weight loss (~3–5 kg at 4–5 years); the biology fights back continuously. C. Lifestyle intervention is ineffective and should not be recommended. D. Lifestyle intervention is more effective than pharmacotherapy for sustained weight loss.

Correct: B

Rationale: Anderson 2001 (PMID 11684524) meta-analysis: ~3 kg average sustained loss at 4–5 years. DPP: lifestyle arm reduced diabetes incidence 58% but average weight loss was ~5.5 kg. Look AHEAD: 8.5% loss at year 1, ~6% at year 9 — meaningful but not transformative. Lifestyle is **necessary infrastructure** for any pharmacotherapy and **sufficient for a minority**; the modal long-term outcome for lifestyle alone is partial regain. The clinical takeaway is not "stop recommending lifestyle" (C is wrong) but rather "lifestyle alone is insufficient for most established-obesity patients, and pharmacotherapy is the rate-limiting input for sustained loss."

Section B — Hormonal axes & receptor pharmacology (questions 5–7)

Question 5

GLP-1 receptor agonists produce weight loss through three principal mechanisms. Which list correctly identifies them?

A. Suppressed thyroid function, enhanced gastric motility, reduced cortisol. B. Slowed gastric emptying, enhanced glucose-dependent insulin secretion, central appetite-suppression via hypothalamic and brainstem GLP-1 receptors. C. Increased leptin sensitivity, decreased ghrelin secretion, accelerated lipolysis. D. Direct fat-burning at adipocyte mitochondria, reduced sleep duration, suppressed glucagon.

Correct: B

Rationale: These are the three core mechanisms of GLP-1 RAs in weight management. Slowed gastric emptying contributes to early satiety and post-prandial glucose blunting. Glucose-dependent insulin secretion improves glycemia without hypoglycemia risk. The central appetite-suppressing effect — via brainstem (NTS) and hypothalamic GLP-1 receptors — is the largest contributor to sustained weight loss, distinct from GI side effects.

Option A is wrong on all three. C confuses GLP-1 mechanisms with other axes. D is fabricated.

Question 6

Amylin receptors are obligate heterodimers requiring co-expression of the calcitonin receptor with which other protein family?

A. RAMPs (receptor activity-modifying proteins): RAMP1, RAMP2, RAMP3. B. GPCRs (G-protein coupled receptors). C. SGLT2 transporters. D. CYP450 enzymes.

Correct: A

Rationale: The amylin receptor is the CTR (calcitonin receptor) paired with one of three RAMPs, generating three subtypes: AMY1 (CTR+RAMP1), AMY2 (CTR+RAMP2), AMY3 (CTR+RAMP3). Without a RAMP, the CTR alone has low amylin affinity. This is why amylin biology is mechanistically distinct from other satiety axes — the RAMP-dependent receptor architecture allows tissue-selective signaling. Cagrilintide and pramlintide engage this system. The pharmacology was reviewed in detail in the M5.1 amylin-axis section.

Question 7

A patient with insulin-resistant phenotype (HOMA-IR > 2.5, fasting glucose 110 mg/dL, elevated triglycerides) is considering between semaglutide and tirzepatide. The strongest mechanistic argument for tirzepatide is:

A. Tirzepatide has a longer half-life than semaglutide. B. Tirzepatide adds dual GIP receptor agonism on top of GLP-1, which contributes additional insulin-secretory potentiation in a glucose-dependent manner and adipose-tissue mechanism activity relevant to insulin-resistant patients. C. Tirzepatide does not require titration like semaglutide does. D. Tirzepatide has no GI side effects.

Correct: B

Rationale: Tirzepatide is a dual GLP-1/GIP receptor agonist. The GIP component contributes insulin-secretory potentiation and has emerging adipose-tissue effects that may explain part of the differential weight-loss magnitude observed in SURMOUNT-5 (tirzepatide 20.2% vs semaglutide 13.7% at 72 weeks). For the insulin-resistant phenotype specifically, the dual-incretin mechanism is the strongest mechanistic argument. Options A, C, D are factually incorrect.

Section C — Trial evidence & decision-making (questions 8–11)

Question 8

SURMOUNT-5 (Aronne 2025, PMID 40855305) is the direct head-to-head trial between tirzepatide and semaglutide for weight management. Which is the correct headline result at 72 weeks?

A. Semaglutide 20.2% vs tirzepatide 13.7%. B. Tirzepatide 20.2% vs semaglutide 13.7% (a 6.5 percentage-point advantage for tirzepatide). C. Tirzepatide and semaglutide were equivalent. D. Tirzepatide was numerically lower but not statistically significant.

Correct: B

Rationale: SURMOUNT-5 is the only direct head-to-head between the two compounds. Tirzepatide produced approximately 6.5 percentage points more weight loss than semaglutide at the doses each had achieved by week 72. This does not mean tirzepatide is the right answer for every patient — cardiovascular outcomes evidence, MASH approval status, cost, and side-effect profile all factor in — but on the question "which produces more weight loss on average," tirzepatide does.

Question 9

A patient with obesity (BMI 33) and established cardiovascular disease is considering semaglutide. The trial that specifically supports the cardiovascular indication is:

A. STEP-1 (Wilding 2021). B. SELECT (Lincoff 2023). C. SURMOUNT-1 (Jastreboff 2022). D. ESSENCE (Sanyal 2025).

Correct: B

Rationale: SELECT (PMID 37952131) demonstrated a 20% reduction in major adverse cardiovascular events (3-point MACE) in patients with obesity (BMI ≥27) and established cardiovascular disease, with semaglutide 2.4 mg weekly. This is a hard cardiovascular outcome, not a surrogate. STEP-1 (PMID 33567185) established the weight-loss efficacy but was not powered for CV events. SURMOUNT-1 was the tirzepatide weight-loss trial. ESSENCE is the semaglutide MASH trial.

Question 10

Per the Ko 2026 systematic review and meta-analysis (PMID 41359966; 48 RCTs, n=94,245), the relationship between GLP-1 receptor agonists and obesity-related cancers (thyroid, pancreatic, breast, kidney) is best characterized as:

A. Strong evidence of increased cancer risk; the class should be avoided in patients with cancer history. B. Moderate-certainty evidence that GLP-1 RAs and dual agonists probably have little or no effect on the risk of these cancers, with the caveat of relatively short trial follow-up. C. The data are too sparse to draw any conclusion. D. GLP-1 RAs are protective against all cancers.

Correct: B

Rationale: "Little or no effect" with moderate certainty across 94,245 patients. Ko 2026 is the most rigorous current synthesis. The MTC/MEN2 boxed warning remains an absolute contraindication (rodent-derived, Bjerre Knudsen 2010 PMID 20203154). The Bezin 2023 (PMID 36356111) French database analysis reports a positive thyroid signal that has not been consistently reproduced and is contextualized by Ko 2026's broader synthesis. The honest framing is B — neither dismissive nor alarmist.

Question 11

A patient with personal history of acute pancreatitis (resolved, 4 years ago) asks about starting a GLP-1 RA. The most appropriate clinical position is:

A. Absolute contraindication — never prescribe. B. The pooled relative risk of acute pancreatitis on GLP-1 RAs is approximately 1.44 (Wen 2025, PMID 40988099). Personal pancreatitis history shifts the risk-benefit toward a different agent class (consider amylin-based or non-incretin alternatives), or careful shared decision-making with intensive monitoring if GLP-1 RA is still pursued. C. No relevant signal — proceed without modification. D. Switch to compounded preparation, which has no pancreatitis signal.

Correct: B

Rationale: Wen 2025 systematic review (62 RCTs, n=66,232): pooled RR for acute pancreatitis 1.44 (95% CI 1.09–1.89) — statistically significant but modest in absolute terms. Personal history is not an absolute contraindication, but it shifts the risk-benefit assessment. A is too restrictive; C is too dismissive; D is incorrect — the pancreatitis signal is a class effect of the molecule, not a function of preparation pathway.

Section D — Safety counseling & shared decision-making (questions 12–13)

Question 12

A reproductive-age woman on semaglutide 2.4 mg weekly is now planning pregnancy. The clinically appropriate washout period before conception attempts is approximately:

A. 2 days (similar to liraglutide). B. 2 months — semaglutide's elimination half-life is approximately 1 week, requiring ~5 half-lives to fully clear. C. 6 months as a precautionary measure. D. No washout needed — semaglutide is pregnancy-safe.

Correct: B

Rationale: Semaglutide's elimination half-life is approximately 1 week; full washout is achieved at ~5 half-lives, ~5 weeks plus a safety margin = roughly 2 months. Liraglutide, with its 13-hour half-life, requires only ~2 days. This difference can be clinically decisive for patients in reproductive years — if pregnancy is on the horizon, liraglutide's much shorter washout may favor that compound. Standard practice when pregnancy occurs or is planned: discontinue.

Question 13

The non-arteritic anterior ischemic optic neuropathy (NAION) signal with semaglutide became labeled by the EMA in May 2025. The most accurate patient counseling framing is:

A. "There's no real risk — the data is too weak." B. "NAION is a recognized but very rare adverse event with semaglutide (on the order of ~1 case per 10,000 person-years). Risk factors include diabetes, OSA, and small optic disc anatomy. If you have predisposing factors we should discuss them; in any case, sudden vision changes warrant same-day ophthalmology evaluation." C. "You should avoid semaglutide entirely." D. "NAION risk doubles every year you stay on the medication."

Correct: B

Rationale: This is compliant patient-counseling phrasing. Acknowledge the signal, contextualize the absolute risk (EMA-classified "very rare"), name the relevant risk factors, establish a clear when-to-seek-care threshold. Dismissive framing (A) loses patient trust when they encounter the topic in social media. Avoidance framing (C) deprives appropriate patients of effective therapy. D fabricates a dose-time relationship not supported by the data.

Section E — Compounded preparations & operational practice (questions 14–15)

Question 14

A patient asks whether compounded semaglutide is "the real thing." The most accurate response is:

A. "Compounded versions contain a different molecule than Wegovy or Ozempic." B. "The molecule (semaglutide) is the same. What differs is the supply pathway: 503A or 503B compounding pharmacy rather than the manufacturer's pre-filled pen. Quality varies between compounding pharmacies and should be vetted (sterility, certificate of analysis, cold-chain, state licensure)." C.

“Compounded preparations are illegal and you should never use them.” D. “Compounded preparations have FDA approval, just like Wegovy.”

Correct: B

Rationale: The molecule is the same; the preparation pathway differs. Quality is highly variable between compounding pharmacies — see Doc 3 (Compounding Pharmacy Quality Audit Checklist) for the practical vetting framework. Marketing claims for the molecule under brand names (Wegovy, Ozempic) are FDA-approved for the manufacturer’s preparation; compounded preparations operate in a different regulatory pathway (503A state-licensed, 503B FDA-registered outsourcing facilities) and the FDA-shortage-list status determines current allowable compounding for these molecules at any given time.

Question 15

The most common patient question at week 3 of GLP-1 RA initiation is typically:

A. “When can I stop the medication?” B. “Is the injection painful?” C. “How do I manage the GI side effects and titration cadence?” D. “Will this cause cancer?”

Correct: C

Rationale: Patients ask about the injection mechanics once (in the office, with the demonstration). By week 3, that’s not the substantive question. The substantive concerns at week 3 are dose-tolerance, GI effects, titration cadence, and side-effect management. The M5.1 lesson explicitly notes that framing self-injection as the major barrier mischaracterizes the actual patient experience; the medication-management conversation is where most clinician time at follow-up should be invested.

Scoring

Section	Question count	Correct
A — Pathophysiology & framing	4	__ / 4
B — Hormonal axes & receptor pharmacology	3	__ / 3
C — Trial evidence & decision-making	4	__ / 4
D — Safety counseling	2	__ / 2
E — Compounded & operational	2	__ / 2
Total	**15**	**__ / 15**

12+ / 15 = passes for CME credit (M5.1 module knowledge check). **10–11 / 15** = recommended to re-watch the M5.1 hormonal-axes and mechanism-class-taxonomy sections before continuing to M5.2. **< 10 / 15** = recommended full M5.1 re-watch before continuing.

References cited in this assessment

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Linked artifacts: M5.1 video lesson · Doc 1 Baseline Labs Checklist · Doc 9 Trial Portfolio Cards · Doc 10 Safety Deep Dive · Doc 3 Compounding Audit Checklist