Optimizing Metabolic Health

Promoting GLP-1 through foundational lifestyle factors, supplementation, or medications

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GLP-1 agonists

Glucagon-like peptide-1 (GLP-1) agonist medications are utilized to enhance metabolic health by improving insulin sensitivity, promoting weight loss, and offering cardiovascular (CV) risk-reduction benefits. (Gad 2024)(Latif 2024) This protocol outlines the use of GLP-1 medications alongside recommendations for nutritional shifts, supplement ingredients, labs, and tools to monitor and evaluate treatment. The primary goal is to mitigate potential adverse effects of GLP-1 medications while providing crucial nutritional support. This comprehensive approach helps to ensure a safe method to both initiating and de-escalating GLP-1 medications.

CV considerations will be called out given the CV risk-reduction benefits of GLP-1 medications; however, for more in-depth support, please refer to the Vascular Health Protocol.

Background

GLP-1 medications mimic the incretin hormone GLP-1, offering significant metabolic benefits by improving insulin sensitivity, promoting weight loss, and reducing CV risk. (Gad 2024) These medications enhance insulin secretion and reduce appetite, making them useful for treating type 2 diabetes and obesity.

Beyond their metabolic benefits, GLP-1 medications support a broader transformational journey towards overall well-being and long-term health improvements. When implemented as part of a comprehensive strategy that addresses foundational aspects of health—nutrition, movement, stress management, and relationships—this holistic approach not only focuses on metabolic health but also empowers patients to achieve lasting positive changes in their overall health and quality of life.

A comprehensive strategy is crucial for metabolic health management—beyond glucose and weight control.

Indications

- Diabetes management
- Improved insulin sensitivity
- Reduced CV risk in patients with metabolic syndrome (MetS)
- Reduced incidence of death from CV causes in patients with pre-existing cardiovascular disease (CVD)
- Weight loss and obesity management (Lincoff 2023)

Contraindications

- Known hypersensitivity to GLP-1 receptor agonists
- Personal or family history of medullary thyroid carcinoma (MTC)
- Patients with multiple endocrine neoplasia type 2 (MEN 2) (DailyMed 2023)

Warnings and precautions

Injection pens

Avoid sharing injection pens. Semaglutide pens should be used exclusively by the individual patient to whom they're prescribed. Even with a new needle, sharing pens between patients can lead to the transmission of infectious agents, including blood-borne pathogens. (DailyMed 2023)

Pancreatitis

Monitor patients for signs and symptoms indicative of pancreatitis, such as severe, persistent abdominal pain that may radiate to the back, with or without accompanying nausea and vomiting. Discontinue semaglutide immediately if pancreatitis is suspected, and evaluate appropriately. (DailyMed 2023)

Diabetic retinopathy

In patients with a history of diabetic retinopathy, be aware that semaglutide may exacerbate retinopathy complications. Regular ophthalmic assessments are recommended during therapy. (DailyMed 2023)

Renal impairment

Renal function should be closely monitored, particularly in patients who experience significant gastrointestinal (GI) adverse reactions, such as nausea, vomiting, or diarrhea, as these can lead to dehydration and worsening renal function. Adjust the dose or discontinue use if necessary. (DailyMed 2023)

Hypersensitivity reactions

Be vigilant for any hypersensitivity reactions, including anaphylaxis and angioedema. In the event of a serious hypersensitivity reaction, discontinue semaglutide immediately and initiate appropriate treatment. Consider the potential for cross-reactivity in patients with a history of hypersensitivity to other GLP-1 receptor agonists. (DailyMed 2023)

Cholelithiasis and gallbladder disease

Patients presenting with symptoms suggestive of gallbladder disease, such as right upper quadrant pain, fever, or jaundice, should be evaluated for cholelithiasis. Appropriate clinical management, including imaging studies, should be pursued as indicated. (DailyMed 2023)

Pregnancy

The use of semaglutide during pregnancy has limited data, and potential risks to fetal development cannot be ruled out. Consider alternative therapies for glycemic control in pregnant patients, and weigh the benefits of semaglutide therapy against potential risks. (DailyMed 2023)

Risk of hypoglycemia with concomitant insulin or insulin secretagogues

Patients who are prescribed semaglutide in combination with insulin or insulin secretagogues (such as sulfonylureas) may face a higher risk of hypoglycemia, including severe cases. To reduce this risk, consider adjusting the dosage of the insulin or insulin secretagogue. Patients should be educated on recognizing and managing the symptoms of hypoglycemia. (DailyMed 2023)

Labs

Schedule recommendations for testing

Re-test biomarkers every 3–6 months using clinical judgment. Clinicians are encouraged to personalize the frequency of biomarker testing to the individual needs of the patient, based on factors such as their current health status, risk factors, treatment response, and overall progress using GLP-1 medications.

Foundational testing

Foundational testing includes essential markers for an initial assessment and routine monitoring of metabolic health.

*For comprehensive metabolic health management, it's essential to test beyond hemoglobin A1C (HbA1c) and incorporate a spectrum of metrics listed below. These metrics provide a more holistic picture of glycemic control, highlight safety concerns, and facilitate timely personalization of management plans.

Test	Recommended range
Fasting blood sugar (FBS)	**Fasting reference interval:** 65–99 mg/dL **Non-fasting reference interval:** 65–139 mg/dL (Quest Diagnostics)
Insulin resistance	**Insulin, intact, LC/MS/MS:** ≤16 uIU/mL **C-peptide, LC/MS/MS:** 0.68–2.16 ng/mL **Insulin resistance score:** ≤66 (Quest Diagnostics)
Two-hour glucose/insulin challenge (in-office test)	**Two-hour plasma glucose level <110 or <140 mg/dL*:** Normal *Depending on the organization **Two-hour plasma glucose level 140–199 mg/dL:** Impaired glucose tolerance **Two-hour plasma glucose level ≥200 mg/dL:** Diabetes (Eyth 2023)
HbA1c	<5.7 % of total hemoglobin (Quest Diagnostics)
Continuous glucose monitoring (CGM)	**Average glucose:** N/A **Glucose management indicator (GMI):** N/A **Time in range (TIR):** 70–180 mg/dL is associated with diabetes complications and outcomes **Time in tight range (TITR):** 70–140 mg/dL (for A1C targets <7%, where TIR is less sensitive to changes in average blood glucose) **Glycemic variability (GV):** ≤36% (target) (Bergenstal 2018)
High-sensitivity C-reactive protein (hs-CRP)	**hs-CRP (mg/L):** • ≤17 years: Not established • >17 years: Optimal <1.0 mg/L **Risk according to AHA/CDC guidelines** (for ages >17 years): • <1: Lower relative CV risk • 1–3: Average relative CV risk • 3.1–10: Higher relative CV risk; consider retesting in 1–2 weeks to exclude a benign transient elevation in the baseline CRP value secondary to infection or inflammation • >10: Persistent elevation, upon retesting, may be associated with infection and inflammation (Quest Diagnostics)

Homocysteine	**Male:** <11.4 umol/L **Female:** <10.4 umol/L (Quest Diagnostics)
Serum uric acid	**Male (mg/dL):** • 13–15 years: 3.1–7 • 16–18 years: 2.1–7.6 • ≥19 years: 4–8 **Female (mg/dL):** • 13–15 years: 2.2–6.4 • 16–18 years: 2.4–6.6 • ≥19 years: 2.5–7 (Quest Diagnostics)
Creatine kinase	**Male (U/L):** • 12 years: <217 • 18 years: <245 • >18 years: 44–196 **Female (U/L):** • 12 years: <143 • 18 years: <143 • >18 years: 29–143 (Quest Diagnostics)
Vitamin D 25-OH	**Vitamin D, 25-OH, total:** 30–100 ng/mL* **Vitamin D, 25-OH, D3:** Not established **Vitamin D, 25-OH, D2:** Not established *25-OHD3 indicates both endogenous production and supplementation. 25-OHD2 is an indicator of exogenous sources, such as diet or supplementation. Therapy is based on measurement of total 25-OHD, with levels <20 ng/mL indicative of vitamin D deficiency, while levels between 20–30 ng/mL suggest insufficiency. Optimal levels are ≥30 ng/mL. (Quest Diagnostics)
OmegaCheck®	≥ 5.5: Low CVD risk level 5.4–3.8: Moderate CVD risk level ≤3.7: High CVD risk level (Quest Diagnostic)

Albumin/ creatinine ratio (urine) (uACR)	**Albumin, urine:** Not established **Albumin/creatinine ratio, random urine:** <30 mcg/mg **Creatinine, random urine (mg/dL):** • Male (>12 years): 20–320 • Female (>12 years): 20–275 (Quest Diagnostics)
Lactate dehydrogenase (LDH)	**Male (mg/dL):** • 11–13 years: 110–250 • 14–17 years: 110–230 • 18–49 years: 100–220 • >49 years: 120–250 **Female (mg/dL):** • 11–13 years: 110–250 • 14–17 years: 110–230 • 18–49 years: 100–200 • >49 years: 120–250 (Quest Diagnostics)
B vitamins	**The following reference ranges apply to individuals ≥18 years (<18 references ranges not available for this micronutrient test):** • Folate: >5.4 ng/mL • Vitamin B1 (thiamine): 78–185 nmol/L • Vitamin B2: 6.2–39.0 nmol/L • Vitamin B3: ≤110 ng/mL • Vitamin B5: <275 ng/mL • Vitamin B6: 2.1–21.7 ng/mL • Vitamin B12: 200–1,100 ng/mL (Quest Diagnostics)

Iron	**Male (mcg/dL):** • 4–19 years: 27–164 • 20–29 years: 50–195 • ≥30 years: 50–180 • 20–49 years: 40–190 • ≥50 years: 45–160 **Female (mcg/dL):** • 4–19 years: 27–164 • 20–29 years: 50–195 • ≥30 years: 50–180 • 20–49 years: 40–190 • ≥50 years: 45–160 (Quest Diagnostics)

Comprehensive metabolic panel (CMP)	**Alanine aminotransferase (ALT):**
	• Male (≥20 years): 9–46 U/L
	• Female (≥20 years): 6–29 U/L
	Aspartate transferase (AST):
	• Male
	  • 20–49 years: 10–40 U/L
	  • ≥50 years: 10–35 U/L
	• Female:
	  • 20–44 years: 10–30 U/L
	  • ≥45 years: 10–35 U/L
	Creatinine (serum):
	• Male:
	  • 13–15 years: 0.4–1.05 mg/dL
	  • 16–17 years: 0.6–1.2 mg/dL
	  • 18–29 years: 0.6–1.24 mg/dL
	  • 30–39 years: 0.6–1.26 mg/dL
	  • 40–49 years: 0.6–1.29 mg/dL
	  • 50–59 years: 0.7–1.30 mg/dL
	  • 60–69 years: 0.7–1.35 mg/dL
	  • 70–79 years: 0.7–1.28 mg/dL
	  • ≥80 years: 0.7–1.22 mg/dL

Comprehensive metabolic panel (CMP) continued	• Female:
	  • 13–15 years: 0.4–1 mg/dL
	  • 16–17 years: 0.5–1 mg/dL
	  • 18–29 years: 0.5–0.96 mg/dL
	  • 30–39 years: 0.5–0.97 mg/dL
	  • 40–49 years 0.5–0.99 mg/dL
	  • 50–59 years: 0.5–1.03 mg/dL
	  • 60–69 years: 0.5–1.05 mg/dL
	  • 70–79 years: 0.6–1 mg/dL
	≥80 years: 0.6–0.95 mg/dL
	Blood urea nitrogen (BUN):
	• Male
	  • 4–19 years: 7–20 mg/dL
	  • ≥20 years: 7–25 mg/dL
	• Female:
	  • 4–19 years: 7–20 mg/dL
	  • ≥20 years: 7–25 mg/dL
	BUN/albumin: 3.4–6.23 mg/g
	Estimated glomerular filtration rate (eGFR): >90 mL/min/1.73m2 (National Kidney Foundation 2022)
	(Quest Diagnostics)

Complete blood count (CBC)	**Neutrophil-to-lymphocyte ratio:** 1–3 **Platelet-to-lymphocyte ratio:** <140 **Lymphocyte-to-monocyte ratio:** 2–4 (Gasparyan 2019)

Comprehensive testing

Comprehensive testing provides an in-depth analysis of advanced markers to detect early signs of metabolic dysfunction, detailed lipid profiling, and inflammatory markers for a thorough evaluation of cardiometabolic risk.

Test	Recommended range
Advanced lipid panel	**Triglyceride (TG)/high-density lipoprotein (HDL) ratio:** <3.8 (target) **Cholesterol/HDL ratio:** <5 **Apolipoprotein B (ApoB):** • <90 mg/dL: Low risk of CV event • 90–119 mg/dL: Moderate risk of CV event • ≥20 mg/dL: High risk of CV event **Lipoprotein(a) (Lp(a)):** • <75 nmol/L: Low risk of CV event • 75–125 nmol/L: Moderate risk of CV event • ≥125 nmol/L: High risk of CV event **Lipoprotein-associated phospholipase A2 (Lp-PLA2):** ≤123 nmol/min/mL **Myeloperoxidase (MPO):** <470 pmol/L **Oxidized lipids (OxLDL):** <60 U/L (Kosmas 2023)

F2-isoprostane/ creatinine ratio	**Urine:** <0.86 ng/mg (target) (Cleveland HeartLab 2013)
Glycoprotein acetylation (GlycA)	<400 µmol/L (Mehta 2020)
Thyroid function tests	**Thyroid-stimulating hormone (TSH) (mIU/L):** • 1–19 years: 0.5–4.3 • ≥20 years: 0.4–4.5 **Free T4 (ng/dL):** • 2–12 years: 0.9–1.4 • 13–20 years: 0.8–1.4 >20 years: 0.8–1.8 **Free triiodothyronine (T3) (pg/mL):** • 2–12 years: 3.3–4.8 • 13–20 years: 3.0–4.7 • >20 years: 2.3–4.2 **Thyroid peroxidase antibodies (TPOAb):** <9 IU/mL **Thyroglobulin antibodies (TgAb):** ≤1 IU/mL • (Quest Diagnostics)
Autoimmune tests	**Islet cell autoantibodies (ICAs):** Negative **Glutamate decarboxylase 65 (GAD-65):** • <5 IU/mL: Negative
Adrenal salivary five-point	• 8–10 a.m.: 0.04–0.56 mcg/dL • 12–2 p.m.: ≤0.21 mcg/dL • 4–6 p.m.: ≤0.15 mcg/dL • 10 p.m.–1 a.m.: ≤0.09 mcg/dL

Lab values indicating prediabetes, insulin resistance, or metabolic syndrome

Lab values indicating prediabetes, insulin resistance, or MetS should be considered indicators of increased risk of cardiometabolic disease progression. (Fahed 2022)

Fasting blood sugar

FBS measures the level of glucose in the blood after an overnight fast, typically 8–12 hours without food or caloric beverages. It's a foundational biomarker used to evaluate glucose metabolism and identify potential insulin resistance, prediabetes, or diabetes. Elevated FBS, defined as levels between 100–125 mg/dL (impaired fasting glucose), indicates impaired glucose regulation and may signal underlying insulin resistance or an increased risk for metabolic disorders. Levels ≥126 mg/dL on two separate occasions are diagnostic for diabetes.

FBS is a simple and reliable test that provides a snapshot of the body's ability to regulate glucose at baseline. Early detection through FBS allows for timely intervention and lifestyle modifications aimed at restoring glucose balance and reducing future metabolic risk.

Insulin resistance

The Cardio IQ® IR Score provides a comprehensive assessment of insulin resistance by measuring both fasting insulin and C-peptide levels in a single test. Validated against the gold-standard insulin suppression test, the Cardio IQ® IR Score offers enhanced accuracy and discrimination of insulin resistance compared to traditional markers, such as the homeostatic model assessment for insulin resistance (HOMA-IR), TG/HDL, and fasting insulin. This enhanced precision makes it an invaluable tool for the early detection, intervention, and management of insulin resistance and associated metabolic disorders. (Abbasi 2018)(Louie 2023)(Quest Diagnostics)

Two-hour glucose/insulin challenge

The oral glucose tolerance test (OGTT), performed in-office, is a valuable tool, when paired with insulin measurements during the test, for revealing early signs of insulin resistance and beta-cell dysfunction before they manifest in HbA1c levels. (Eyth 2023)(Sulaiman 2010)

Hemoglobin A1c

HbA1c reflects the average blood glucose levels over the previous 2–3 months. However, it fails to capture daily fluctuations and specific patterns critical for comprehensive diabetes management, which can be misleading if used in isolation. While HbA1c is a valuable tool for assessing long-term blood glucose control, it has notable limitations that necessitate additional metrics for a comprehensive understanding of glucose and metabolic health management. (Beck 2021)(Chehregosha 2019)

Continuous glucose monitoring

CGM is encouraged throughout this protocol to monitor the key metrics of metabolic health management listed below, which provide objective data and real-time insights. This is crucial for adjusting management plans to mitigate risks and enhance patient safety.

- **Average glucose** aids in understanding how daily glucose levels align with the average over a specific time period.
- **Glucose management indicator (GMI)** translates CGM data into an estimated HbA1c value that reflects a more real-time estimation of glycemic control.
- **Time in range (TIR) and time in tight range (TITR)** are critical indicators of overall glucose management, with higher TIR and TITR values reflecting better glycemic control and being associated with a reduced risk of diabetes complications, such as CVD, neuropathy, and hypoglycemia.
- **Glucose variability (GV)** refers to fluctuations in blood glucose levels throughout the day. High GV, associated with increased oxidative stress and inflammation, should prompt clinicians to identify and address unstable glucose patterns that HbA1c alone may miss.

Advanced lipid panel

An advanced lipid panel, which measures the number and size of low-density lipoprotein (LDL) particles, can indicate changes in lipid oxidation, a rise in TG production, and shifts in lipoprotein concentrations. These changes can be due to an increase in circulating free fatty acids (FFAs), which is a common result of insulin resistance. (Fahed 2022)

A higher TG/HDL ratio has been correlated with muscle mass in patients with type 2 diabetes mellitus. (Fu 2023)

Inflammation and oxidative stress markers

Markers of inflammation and oxidative stress are associated with increased cardiometabolic risk.

Serum uric acid

Although uric acid has the potential for antioxidant support, hyperuricemia is associated with an increased risk of metabolic diseases such as MetS, insulin resistance, and metabolic dysfunction-associated steatotic liver disease (MASLD). (Armborst 2021)

Homocysteine

Hyperhomocysteinemia is associated with MetS and obesity due to vascular and DNA damage resulting from oxidative stress. Deficiencies in folate and vitamin b12 can contribute to elevated levels of homocysteine. (Ulloque-Badaracco 2023)

F2-isoprostanes/creatinine ratio

Urinary F2-isoprostanes (F2-isoPs) are validated biomarkers of human oxidative status, indicating the generation of free radicals, particularly reactive oxygen species (ROS). Traditionally, elevated levels of systemic F2-isoPs are seen as markers of harmful oxidative stress, linking obesity to CV risk. However, recent research suggests that higher urinary F2-isoPs may also predict lower risks of weight gain and type 2 diabetes, highlighting a protective metabolic trait. This dual role can be explained by the connection between mitochondrial oxidative metabolism and urinary F2-isoPs, primarily driven by fatty acid (FA) oxidation, which produces ROS. (Il'yasova 2015)

Glycoprotein acetylation

GlycA is a biomarker of systemic inflammation that may be a predictor of CVD risk and a quantitative tool for assessing the effectiveness of anti-inflammatory treatments aimed at reducing CVD risk. (Ballout 2020)

Liver enzymes

Alanine aminotransferase and aspartate transferase

ALT is primarily a liver enzyme, and lower levels have been linked to reduced muscle mass and sarcopenia. (Il'yasova 2015)

AST is a biomarker for liver and skeletal muscle injury. Elevated AST levels may be associated with sarcopenia; however, these levels can also be influenced by other organs due to the enzyme's wide distribution in the body.

Elevations in all liver enzymes have been associated with MetS. Liver changes associated with hepatic steatosis may contribute to insulin resistance and be an early sign of metabolic diseases. (Raya-Cano 2023)

Increasing AST/ALT ratios (>1.35) have been significantly associated with a higher prevalence of sarcopenia and an increased risk for low muscle mass in some populations. Conversely, these elevated ratios are linked with a lower prevalence of obesity, hypertriglyceridemia, and diabetes mellitus. (He 2022)(Ma 2022)

Gamma-glutamyltransferase

Gamma-glutamyltransferase (GGT) is an enzyme primarily found in the liver and serves as a key biomarker for various health conditions. Elevated GGT levels are linked to an increased risk of type 2 diabetes and MetS. High GGT levels are also associated with increased body mass index (BMI), TGs, glucose levels, blood pressure, and LDL cholesterol, while being inversely related to HDL cholesterol. Additionally, GGT acts as an indicator of alcohol and toxin exposure due to its role in breaking down glutathione. (Raya-Cano 2023)

Thyroid markers

Thyroid function tests are crucial for assessing metabolic health, as thyroid hormones influence various metabolic processes. Both hyperthyroidism and hypothyroidism can impair insulin sensitivity. Hypothyroidism is linked to decreased glucose uptake and increased peripheral insulin resistance. Hyperthyroidism can lead to elevated blood glucose levels due to increased hepatic glucose production and accelerated insulin degradation. (Teixeira 2020)

Thyroid-stimulating hormone

Elevated TSH levels (>2.5 mIU/L) are associated with increased BMI, waist circumference, insulin resistance (HOMA-IR), and dyslipidemia, particularly higher TGs and lower HDL cholesterol. Higher TSH levels within the normal range are linked to a greater prevalence and severity of MetS.

Free thyroxine and free triiodothyronine

Lower free T4 and free T3 levels are connected to increased body fat, impaired glucose metabolism, obesity, and higher insulin resistance. Higher free T3 levels are positively associated with components of MetS, such as elevated fasting plasma glucose and TGs.

Thyroid antibodies

The presence of thyroid antibodies (TPOAb, TgAb) can indicate autoimmune thyroid diseases that further complicate metabolic conditions, contributing to an increased risk of MetS.

Creatine kinase

Creatine kinase is an enzyme found in the heart, brain, and muscles. It's primarily derived from type 2 skeletal muscle fibers, which are characterized by low glucose uptake and reduced mitochondrial oxidation. These muscle fibers are often associated with obesity and insulin resistance. (Al-Hail 2019)(Haan 2017)

Creatine kinase levels are dependent on age, sex, and muscle mass. (Kim 2021) Elevated levels of creatine kinase have been associated with increased muscle activity, damage, or stress, such as physical activity or a myocardial infarction. Intense exercise and eccentric strength training have a greater effect on raising creatine kinase levels compared to leisurely physical exercise. (Bekkelund 2023)

In a non-diabetic population, there's a significant association between elevated levels of creatine kinase and elevated HbA1c.

In patients with type 2 diabetes mellitus, creatine kinase is associated with BMI and fasting plasma glucose and inversely correlated with low muscle mass. (Hu 2023)

Complete blood count

Insulin resistance is linked to inflammatory processes that activate circulating white blood cells, such as neutrophils and monocytes, which contribute to the secretion of inflammatory cytokines. During these conditions, a decreased lymphocyte count is often observed.

Recent evidence highlights the significance of peripheral blood cell biomarker to HDL cholesterol ratios (e.g., neutrophil to HDL-C ratio, lymphocyte to HDL-C ratio) in assessing inflammation. These ratios are particularly useful for predicting MetS in individuals with severe obesity. The most affected hematological parameters in an inflammatory state are increased neutrophils and reduced HDL cholesterol, with the ratio being influenced by the increase in neutrophil count and decrease in HDL-C values in individuals with MetS. This underscores the importance of CBC-derived inflammation indexes in understanding and predicting MetS severity. (Marra 2024)

The following ranges may be associated with inflammation:

- Neutrophil/lymphocyte: >1.6 (recommended: 1.5)
- Platelet/lymphocyte: >140 (recommended: <140)
- Lymphocyte/monocyte: <3 (recommended: >4)

Comprehensive metabolic panel

A CMP is essential for monitoring metabolic and muscle health. It provides critical information on glucose levels, electrolyte and fluid balance, kidney and liver function, and protein levels. For metabolic health, a CMP assesses insulin resistance, liver enzymes, and electrolyte imbalances related to hypertension. For muscle health, it includes markers like creatinine and BUN, which indicate muscle breakdown and kidney function, respectively. (Fahed 2022)(Gounden 2024)

The ranges in the following table may be associated with inflammation.

Creatinine	**Men:** >1.3 mg/dL **Women:** >1.0 mg/dL
BUN	>10 mg/dL
BUN/albumin	<4.0 mg/g
eGFR	**Men:** <100 mL/min/1.73m2 **Women:** <90 mL/min/1.73m2

Albumin/creatinine ratio (urine)

Research has shown that uACR may be correlated with cardiometabolic measures such as waist circumference, HDL cholesterol, adiponectin, and insulin sensitivity. Among initially normoglycemic, normotensive individuals with parental diabetes, those in the upper quartiles (<30 mg/g) of baseline uACR levels were more likely to progress from normoglycemia to pre-diabetes compared with those at the lowest quartile. (Everett 2024)

Lactate dehydrogenase

Elevated LDH levels are a general indicator of acute and chronic diseases, including cancer progression and muscle health conditions such as muscular dystrophy. In the context of metabolic health, elevated LDH reflects the muscle response to training and can also indicate issues like myocardial infarction and metabolic disturbances, making it a valuable biomarker for assessing overall health.

Higher serum LDH (sLDH) levels have been strongly linked to frailty components such as slow walking, weakness, exhaustion, and low physical activity, particularly in individuals with MetS. This correlation suggests that sLDH is a valuable biomarker for assessing both metabolic and muscle health, highlighting its significance in predicting overall health risks. (Chen 2021)(Farhana 2023)

B vitamins

Lower serum concentrations of folate, vitamin B6, and vitamin B12 have been associated with an increased risk of developing MetS. (Zhu 2023)

Vitamin D 25-OH

Serum vitamin D levels are inversely associated with the risk of abdominal obesity in adults. Each 25 nmol/L increase of serum vitamin D may be associated with an 8% reduced risk of abdominal obesity. (Hajhashemy 2021)

Vitamin D deficiency has also been shown to be associated with increased BMI and inflammation, which may have adverse effects on metabolic health when obesity is also a contributing factor. (Gariballa 2022)

Iron panel

Adults with obesity are at increased risk for iron deficiency. Transferrin saturation has been shown to be lower in individuals with obesity and an expanded waist circumference compared to those with a smaller waist circumference. Ferritin has been shown to be positively correlated with visceral fat area as well as waist-to-hip ratio independent of BMI. (Hilton 2023)

OmegaCheck®

An OmegaCheck® measures omega-3 polyunsaturated fatty acids (PUFAs) and total FA levels in whole blood and an omega-3 index in red blood cells (RBCs). These markers are linked to diabetes outcomes, with higher omega-3 levels associated with lower risk of type 2 diabetes mellitus. (Chaaba 2023)(Ma 2021)

Autoimmune markers

Positive ICAs and glutamic acid decarboxylase (GADA) have been shown to be predictive for potential progression towards an insulin-dependent state after a diagnosis of diabetes. Levels of anti-islet autoantibodies decrease with disease duration and can become negative, highlighting the importance of early diagnosis. (Kawasaki 2023)

Adrenal salivary five-point

Stress-related elevations in cortisol can contribute to hypothalamic-pituitary-adrenal (HPA) axis dysregulation. This can correlate with body composition shifts indicating metabolic disease, such as increased visceral fat, decreased lean body mass, and loss of bone mineral density. (Cvijetic 2022)

Diagnostics: Monitoring

Body composition analysis is useful for quantifying body fat and its distribution in the body, which is a significant risk factor for cardiometabolic diseases. Adipose tissue stored in the abdominal region is linked to obesity-related complications and mortality. In contrast, adipose tissue in the gluteofemoral region is associated with lipid and glucose markers that are protective against metabolic diseases, even after considering total body fat. (Goossens 2017)

Bioelectrical impedance analysis scales

Bioelectrical impedance analysis (BIA) scales (Nokia/Withings) estimate body composition parameters based on body fluid volume measurement: total body water (TBW) and fat-free mass (FFM), which encompass bone mineral content (BMC), extracellular water, intracellular water, and visceral protein. (Marra 2019)

Pros

- Non-invasive, accessible (Heidari 2022)
- Provide the ability to follow body composition shifts over time (Marra 2019)
- Can be incorporated with tape-measured waist circumference for assessment of android fat (Burridge 2022)

Cons

- Unable to detect body fat distribution (Heidari 2022)
- Influenced by physical exercise, food or fluid intake, and other conditions that can modify an individual's hydration level (e.g., dehydration/edema) (Marra 2019)

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DEXA) (InBody) is the gold standard for measuring muscle mass. Though DEXA is primarily used to assess bone health, total-body DEXA scans can provide accurate estimates of BMC, fat mass (FM), and lean body mass (LBM) throughout the body via the measurement of low-emission X-ray beams as they pass through body tissues. (Marra 2019)(Yi 2022)

Pros

- Indirect measurement that provides exact body composition measurements and distributions (Heidari 2022)

Cons

- Primarily used in research and may not be practical
- Does not assess muscle quality
- Technical expertise required (Heidari 2022)
- Limit to two body scans per year (Marra 2019)
  - Effective radiation dose (1–7 μSv ~1–10% of chest X-ray radiation dose)

Continuous glucose monitors

CGMs (Abbott Freestyle Libre, Dexcom Stelo) continuously measure glucose concentrations in the subcutaneous interstitial fluid. (Azulay 2022)

Technology/remote monitoring options

The Oura Ring is a wearable device designed to track various health metrics, including heart rate variability (HRV), physical activity, and sleep patterns, making it a user-friendly tool for patients looking to comprehensively monitor and optimize their cardiometabolic health. (Azulay 2022)

HRV is the variation in time intervals between heartbeats, making it a crucial indicator of autonomic nervous system function. Higher HRV typically signifies better autonomic function, reflecting a well-balanced stress response system. Studies show that reduced HRV has been observed in individuals with MetS and is associated with an increased risk of CVD.

Risk factors

Genetics and family history

Genetic polymorphisms, single-nucleotide polymorphisms (SNPs), can result in dysfunctional metabolic pathways, particularly when these genetic variations interact with dietary factors. Such variations can predispose certain individuals to developing metabolic disorders. (Butcko 2024)

Identifying genetic predispositions, particularly SNPs, that mediate weight gain by affecting responses to high-saturated-fat diets, as well as genes that regulate carbohydrate and lipid metabolism, energy management, and digestive enzymes, improves risk stratification and management of metabolic diseases through personalized nutritional recommendations. (Mansour 2024)

Family history is a strong risk factor for diabetes as a result of metabolic dysfunction, which is independent of lifestyle and other metabolic factors. (Ye 2022)

Body composition

“Apple-shaped” bodies, characterized by excess central or abdominal visceral adipose tissue, are associated with an increased risk of developing insulin resistance compared to those with “pear-shaped” bodies characterized by subcutaneous fat accumulation. (Fahed 2022)

Foundational risk factors and interventions

Nutrition

Risk factors

The standard American diet is characterized by a high consumption of ultra-processed foods and is associated with an increased risk of developing metabolic diseases such as diabetes and congenital heart disease. (Christodoulou 2022)

Glycemic load is calculated by multiplying a food’s glycemic index by its carbohydrate content, with higher values indicating more refined grains, starches, and sugars. (Micha 2017)

Glycemic load is an important dietary risk factor for metabolic disease. Evidence shows that nutrition patterns with a lower glycemic load can reduce postprandial blood sugar spikes and improve long-term glycemic control and therefore metabolic health. (Chiavaroli 2021)

Interventions

The Mediterranean diet

The Mediterranean diet (MD) is characterized by an increased intake of olive oil, fruits, vegetables, legumes, nuts, and non-refined cereals. This dietary pattern includes an allowance of fish and poultry and low to moderate intake of dairy products, alcohol, red meat, and desserts.

Meta-analyses reveal that the MD is associated with beneficial changes in biomarkers of metabolic dysfunction (e.g., body weight, BMI, waist circumference, glucose, insulin, HOMA-IR, advanced lipid profiles, hepatic function tests, and inflammatory markers). (Papadaki 2020) These biomarker changes are associated with a reduced intake of saturated fats, amino acids, and calories, and an increase in phytochemicals and gut microbiota-produced metabolites. (Tosti 2018)

The macronutrient breakdown of the MD emphasizes a balance of healthy fats, moderate protein, and complex carbohydrates. Healthy fats, particularly from olive oil, nuts, and fatty fish, make up approximately 35–40% of total daily calories, with a focus on monounsaturated and omega-3 fats. Carbohydrates, primarily from whole grains, legumes, vegetables, and fruits, constitute around 45–60% of the diet, providing fiber and essential nutrients. Protein, derived from lean sources like fish, poultry, legumes, and dairy, contributes about 15–20% of the daily caloric intake, with limited consumption of red meat. Include a source of lean protein with each meal (8–12 oz per day), and choose lean, free-range, grass-fed, organically grown meats. Non-GMO plant proteins and wild-caught fish is preferred.

This macronutrient profile supports cardiovascular health, promotes anti-inflammatory effects, and aids in metabolic regulation. (Ge 2020)(Willett 1995)

Fasting

Fasting and its variations have gained attention for their potential health benefits. Intermittent fasting typically involves cycles of eating and fasting over specified periods, while time-restricted eating limits food intake to a certain window each day, without calorie restriction. Fasting-mimicking diets simulate the effects of fasting through low-calorie, nutrient-specific meals over several days. These interventions have been studied for their impacts on metabolic health, inflammation, and longevity, but healthcare providers should carefully assess patient suitability, particularly in individuals with metabolic disorders or those at risk for disordered eating.

Fasting: Fasting is the voluntary abstention from all or most food and drink for a specific period, typically for health, religious, or spiritual reasons. It can range from a few hours to several days or longer.

Intermittent fasting (IF): IF is a dietary pattern that alternates between periods of eating and fasting, usually in a cyclical manner. Common methods include the 16:8 method (16 hours fasting, eight hours eating) or alternate-day fasting.

Time-restricted eating (TRE): TRE is a form of intermittent fasting where food intake is limited to a specific time window each day, such as 8–12 hours, without necessarily changing the overall caloric intake or type of food consumed.

Fasting-mimicking diet (FMD): The FMD is a diet designed to mimic the effects of fasting while still providing essential nutrients. It typically involves consuming low-calorie, plant-based meals over a few days to induce the physiological benefits of fasting without complete food deprivation. (Soliman 2022)

Movement

Risk factors

Sedentary activity for four or more hours daily has been associated with an increased risk of MetS, independent of physical activity. (Deng 2024)(Wu 2022)

Interventions

Resistance training to promote lean muscle mass has been associated with reduced body fat percentage, body fat mass, and visceral fat in healthy adults. (Wewege 2022)

When combined with high-intensity aerobic training, high-load resistance training can have beneficial effects for reducing abdominal adiposity, increasing lean body mass, increasing cardiorespiratory fitness, and promoting overall metabolic health. (O'Donoghue 2021)

Sleep

Risk factors

Obstructive sleep apnea (OSA) may contribute to the development of visceral adiposity, which is associated with metabolic diseases such as MetS. These body composition shifts may be related to hypoxia-reoxygenation cycles that disrupt sleep throughout the night. (Chasens 2021)

Misaligned sleep, insomnia, and other sleep disorders have also been shown to negatively affect metabolic factors such as adipose tissue distribution and glucose control.

Interventions

Those with normal sleep (7–8 hours per day) were shown to have a lower risk for MetS compared to those with five hours or less and nine hours or more of sleep per day. (Chasens 2021)

Correcting sleep apnea is critical, as hypoxia is a major driver of mitochondrial dysfunction, inflammation, and insulin resistance.

In addition, encourage better sleep by:

- Eating three or more hours before bedtime
- Supporting the circadian rhythm
- Wearing blue light-blocking glasses at night
- Getting exposure to morning light/sunshine

Stress

Risk factors

Adults who experience psychological stress may have an increased risk of MetS compared to adults who experience less stress. (Kuo 2019)

Interventions

Low levels of or no stress may be associated with a reduced risk of MetS. (Deng 2024) Stress management interventions commonly involve mindfulness practices, such as meditation and deep breathing, alongside cognitive behavioral therapy (CBT) to help patients reframe maladaptive thought patterns. Incorporating physical activity, particularly yoga or aerobic exercise, can enhance relaxation and mood regulation.

Social

Risk factors

Loneliness as a result of social disconnection may be perceived as a chronic psychosocial stressor resulting in an overactive HPA axis, mitochondrial dysfunction, and ultimately metabolic diseases such as MetS. (Ahmed 2023)

Interventions

Research shows an association between social connectedness and a reduced risk of obesity and hypertension, highlighting the protective impact of social integration across life stages. (Yang 2016) Strategies to improve social connection include encouraging participation in group activities or community events, which can foster a sense of belonging. Healthcare providers can also promote active listening and empathy skills to enhance interpersonal relationships. Additionally, leveraging technology for virtual meetups and support groups can be valuable for individuals who face barriers to in-person socializing.

Foundational supplementation

Protein

Dosing: Start with a general dose of 10–20 g daily of plant-based or whey protein (although dosages are typically in the 20–40 g range)

Healthy adults engaging in minimal physical activity should aim for at least 0.8 g of protein per kg of body weight per day to meet the recommended dietary allowance (RDA) of protein to avoid deficiency. This translates to about 10–15% of total daily energy expenditure.

Daily protein intake should be adjusted depending on age, physical activity, and metabolic health goals. Studies suggest that a high-protein diet consisting of 1.07–1.6 g of protein per kg of body weight daily (27–35% of total daily energy expenditure) provides enhanced weight-loss effects while preserving FFM. (Bray 2024)(Moon 2020)

GLP-1 secretion is enhanced by all forms of dietary proteins—from whole proteins to peptides and amino acids—each interacting with unique or unknown cellular mechanisms based on their structure. (Hira 2021)(Meek 2016)(Miguéns-Gómez 2021)(Volpi 2001)

Glutamine

Dosing: 15–30 g daily

A 15–30 g dose is required to leverage glutamine's beneficial metabolic effects as a GLP-1 enhancer. (Meek 2016)

Multivitamin/multimineral

Dosing: Dosing may vary depending on the specific product and should be tailored to the individual's nutritional needs and goals, such as nutrient repletion or metabolic support. Healthcare providers should consult product-specific guidelines and adjust the dosage based on the patient's unique requirements and response.

Multivitamin and multimineral supplements can provide essential nutrients that may be deficient in individuals with MetS, potentially improving overall metabolic health and aiding in the management of related conditions such as insulin resistance, dyslipidemia, and hypertension. Judicious supplementation may support metabolic functions, enhance antioxidant defense, and promote cardiovascular health, offering a valuable addition to lifestyle and dietary interventions to help manage metabolic disorders. (Blumberg 2018)

EPA/DHA

Dosing: 2 g combined daily (adjust dose based on testing)

Omega-3 FAs may offer therapeutic benefits by minimizing muscle loss and inflammation associated with secondary sarcopenia through its ability to modulate proteolytic pathways that result in skeletal muscle regeneration. (Jimenez-Gutierrez 2022)(Smith 2012)

Soluble fiber

Dosing: 5–10 g daily

Soluble fibers, including guar gum and larch arabinogalactan, can support metabolic health by moderating energy intake, stabilizing postprandial blood glucose levels, and improving satiety, ultimately addressing risk factors for obesity, hyperglycemia, and hypercholesterolemia. These ingredients are resistant to digestion and promote beneficial GI microflora and short-chain fatty acid (SCFA) production, supporting a healthy gut environment that favors comprehensive metabolic health. (den Besten 2015)(Dion 2016)(Kim 2002)(Wu 2023)

Vitamin D3+K2

Dosing: 5,000 IUs (adjust dose based on testing) plus 25–95 mcg daily (depending on dose of vitamin D)

Vitamin D+K supplementation is linked to improved metabolic health, enhancing GLP-1 levels and bone metabolism. (Kuang 2020)(Pazarci 2020)(Zhang 2021)

Specialty supplements

Amarasate®

Dosing: 1x125 mg once daily for two days, increasing to 2x125 mg twice daily, one hour before a main meal

Amarasate® has been shown to stimulate the release of the body's natural appetite suppressing hormones, GLP-1 and cholecystokinin (CCK), at 600% above base level and peptide YY (PYY) at 400% (note for behavioral change, the increase must be above 350%). This level has been clinically shown to reduce hunger by 30%, cravings by 40%, and subsequent calorie intake by an average of 18% after one hour.

This provides an effective and affordable, natural appetite-control mechanism that contrasts with the constant and supra-physiological hormone levels achieved by current anti-obesity medications, with further upcoming clinicals aiming to further validate its efficacy for weight loss. (Walker 2019)(Walker 2022)(Walker 2024)

Muscle protection

Creatine monohydrate

Dosing: 5 g daily

Creatine can enhance metabolic health by effectively reducing immediate muscle damage within the first 96 hours following exercise, promoting a faster and more effective recovery. (Harmon 2021)(Kreider 2021)(Smith-Ryan 2021)(Wu 2022)

Strength combination

Beta-hydroxy-beta-methylbutyrate

Dosing: 2,000 mg daily

Beta-hydroxy-beta-methylbutyrate (MyHMB®) is a metabolite of the essential amino acid leucine. It has been shown to effectively mitigate age-related declines in lean mass, while also enhancing muscle strength and functionality in older adults. These benefits may be enhanced with vitamin D3 supplementation. (Flakoll 2004)(Rathmacher 2020)(Wilson 2008)

Calcium

Dosing: 240 mg daily

An increase of 300 mg daily in calcium intake is associated with a 7% reduction in the relative risk of developing MetS, highlighting calcium's potential role in improving metabolic health. Additionally, calcium supports muscle protection by promoting proper muscle function, which is particularly beneficial in managing metabolic diseases. (Eshima 2021)(Han 2019)(Kim 2020)

Epicatechin (green tea leaf extract)

Dosing: 400 mg daily

Found in dark chocolate, green tea, and certain fruits, this flavanoid has been shown to promote muscle growth and enhance exercise performance through mechanisms that include inhibiting myostatin and supporting nitric oxide production. (Mafi 2017)(McDonald 2015)(Ramirez-Sanchez)

PurpleForce® purple tea (*Camellia sinensis*) leaf extract

Dosing: 100 mg daily

PurpleForce® contains anthocyanins, catechins, flavonoids, and other polyphenols that may improve antioxidant activity, supporting muscle recovery and mitigating muscle damage. (Shimoda 2015)

AstraGin® (*Astragalus membranaceus and Panax notoginseng*)

Dosing: 50 mg daily

Containing extracts of *Astragalus membranaceus* and *Panax notoginseng*, AstraGin® supports improved absorption of amino acids, vitamins, and minerals, while also supporting the integrity of the intestinal barrier. (Chang 2022)

Senactiv® (*Panax notoginseng* and *Rosa roxburghii* extracts, *Astragalus membranaceus* and *Panax notoginseng* root extracts)

Dosing: 50 mg daily

Containing extracts of *Panax notoginseng* and *Rosa roxburghii*, Senactiv® supports muscle growth and recovery by enhancing mitochondrial function and reducing oxidative stress. (Wu 2019)(Wu 2019)

Clinical scenario A:

Fasting, intermittent fasting, time-restricted eating, fasting-mimicking diet

This protocol is centered on changing "how" food is consumed, with a focus on dietary timing and cultivating mindfulness around eating. The benefits of fasting and TRE are harnessed through a food-first approach, and supplementation is provided as a supportive tool when necessary. The aim is to ensure accessibility while fostering long-term, sustainable improvements in metabolic health.

Fasting and other specialty nutritional interventions, such as TRE and the fasting-mimicking diet, have shown significant benefits for cardiometabolic health. These approaches can improve metabolic markers, reduce inflammation, enhance the oxidative stress response, and positively influence gut microbiome composition, thereby supporting overall metabolic health. (Zhang 2023)

Metabolic processes involved in fasting include:

- Decreased inflammation
- Increased antioxidant production
- Increased DNA repair
- Activated autophagy
- Normalized insulin and glucose
- Increased BDNF (neuroplasticity)
- Metabolic flexibility (metabolic switching between utilizing glucose and FA-derived ketones as fuel sources for the body) (Vasim 2022)(Wang 2022)

Fasting options

Fasting type	Description
Intermittent fasting	Follow an eating pattern that regularly cycles between periods of fasting and periods of normal eating. (Parveen 2022)
Time-restricted eating	Implement a daily fasting period lasting less than 24 hours, with food intake confined to a designated eating window. Typically, fasting periods span 12–18 hours, followed by eating windows of 6–12 hours. TRE can also be achieved by consuming one meal a day (OMAD), fasting for 23 hours and eating during a brief window. (Parveen 2022)

5:2	Engage in a 24-hour fast twice weekly. On two additional days, adopt a very-low-calorie diet of 500–600 calories per day. (Parveen 2022)

Prolonged fasting	Prolonged fasting is a five-day nutrition program that mimics the metabolic processes of prolonged fasting (a fasting period exceeding 24 hours) without completely eliminating food.
	The following steps outline key considerations for integrating a prolonged fasting protocol with a weekly GLP-1 dosing regimen, focusing on ensuring patient safety, monitoring, and optimizing outcomes during the fasting period:
	• Assess readiness:
	  • Pick a start date that aligns with the weekly GLP-1 dose.
	  • Reduce the weekly dose by 50% while doing a prolonged fast to reduce side effects.
	  • Monitor blood glucose with CGM.
	• Review program.
	• Review and understand the BIA.
	• Review potential side effects.
	• Review food reintroduction.
	• Review safe exercise and movement during prolonged fasting. (Parveen 2022)

Foundational supplementation

Ingredient	Dosing
Protein	Start with a general dose of 10–20 g daily of plant-based or whey protein (although dosages are typically in the 20–40 g range) (Parveen 2022)
Glutamine	A 15–30 g dose is required to leverage glutamine's beneficial metabolic effects as a GLP-1 enhancer. (Parveen 2022)
Multivitamin/ multimineral	Dosing should be adjusted by the healthcare provider based on the individual's nutritional needs and metabolic goals, with consideration of product-specific guidelines. (Parveen 2022)
EPA/DHA	2 g combined daily (adjust dose based on testing) (Parveen 2022)
Soluble fiber	5–10 g daily (Parveen 2022)
Vitamin D3+K2	5,000 IUs (adjust dose based on testing) plus 25–95 mcg daily (depending on dose of vitamin D) (Parveen 2022)

Specialty supplements

Amarasate®

Dosing: 1x125 mg once daily for two days, increasing to 2x125 mg twice daily, one hour before a main meal

Fasting regimen	Dosing
Reduced calorie days during alternate day and 5:2 fasting (500–600 calories per day)	1x125 mg once daily for two days, increasing to 2x125 mg twice daily, one hour before a main meal (Parveen 2022)
Time-restricted eating	1x125 mg to 2x125 mg during fasting periods at four-hour intervals (e.g., If the TRE window is from 12–8 p.m., take Amarsate® in the morning.) (Parveen 2022)
Water-only fasting	1x125 mg to 2x125 mg an hour before normal meal times (Parveen 2022)

Muscle protection

Ingredient	Dosing
Creatine monohydrate	5 g daily (Parveen 2022)
Strength combination:	
MyHMB®	2,000 mg
Calcium	240 mg
Epicatechin	400 mg
PurpleForce®	100 mg
Senactiv®	50 mg
AstraGin®	50 mg (Parveen 2022)

Clinical scenario B:

Complementary approaches to metabolic health

For patients for whom GLP-1 medications and fasting are inaccessible, this protocol offers an alternative approach through the strategic use of supplementation. Key metabolic processes, such as appetite regulation and glucose management, are targeted to replicate the benefits of GLP-1 therapy. This approach provides an effective pathway for optimizing metabolic health when other methods are not available.

Foundational supplementation

Ingredient	Dosing
Protein	Start with a general dose of 10–20 g daily of plant-based or whey protein (although dosages are typically in the 20–40 g range) (Parveen 2022)
Glutamine	A 15–30 g dose is required to leverage glutamine's beneficial metabolic effects as a GLP-1 enhancer. (Parveen 2022)
Multivitamin/ multimineral	Dosing should be adjusted by the healthcare provider based on the individual's nutritional needs and metabolic goals, with consideration of product-specific guidelines. (Parveen 2022)
EPA/DHA	2 g combined daily (adjust dose based on testing) (Parveen 2022)
Soluble fiber	5–10 g daily (Parveen 2022)
Vitamin D3+K2	5,000 IUs (adjust dose based on testing) plus 25–95 mcg daily (depending on dose of vitamin D) (Parveen 2022)

Specialty supplements

Ingredient	Dosing
Amarasate®	1x125 mg once daily for two days, increasing to 2x125 mg twice daily, one hour before a main meal (Parveen 2022)
Muscle protection	
Creatine monohydrate	5 g daily (Parveen 2022)
Strength combination:	
MyHMB®	2,000 mg daily
Calcium	240 mg daily
Epicatechin	400 mg daily
PurpleForce®	100 mg daily
AstraGin®	50 mg daily
Senactiv®	50 mg daily (Parveen 2022)

Clinical scenario C:

Lowest effective dose GLP-1 medication and de-escalation

This protocol combines GLP-1 medication with lifestyle interventions and supplementation, aiming to minimize dependence on pharmacotherapy. The lowest effective dose of GLP-1 medication is pursued while reinforcing the lifestyle changes and nutritional support required for sustaining metabolic health independently over time.

Lowest effective dose of GLP-1 prescription

Titrate to the lowest effective dose.

Note: Initial dose of 0.5 mg weekly is intended to reduce GI symptoms and allow the body to adjust to this medication; it does not provide effective glycemic control.

Treat-to-target GLP-1 agonist titration schedule

Name of medication	1st dosage	28 days	1st titration	28 days	Final dosage
Liraglutide*	0.6 mg subcutaneously daily	→	1.2 mg subcutaneously daily	→	1.8 mg subcutaneously daily
Semaglutide**	0.25 mg subcutaneously once per week	→	0.5 mg subcutaneously once per week	→	1 mg subcutaneously once per week After four weeks, the dose can be increased to 2 mg once per week.

- To optimally utilize this treat-to-target table, self-monitoring of blood glucose (SMBG) should be done fasting pre-breakfast.
- Patients should be titrated through above dosage schedules until SMBG target is attained or until the maximum recommended and tolerated dose is reached.
- * **Note:** The lower initial dose (0.6 mg daily) is intended to reduce GI symptoms; it does not provide effective glycemic control. If GI symptoms persist can continue at 0.6 mg for up to four weeks.
- **May increase further to 2 mg once weekly after four weeks on the 1 mg per week dose if needed to achieve glycemic goals. **Note:** The lower initial dose (0.25 mg weekly) is intended to reduce GI symptoms; it does not provide effective glycemic control. If GI symptoms persist can continue at 0.6 mg for up to four weeks.
- *, ** Liraglutide and semaglutide are contraindicated in gastroparesis, MEN-2, and known medullary thyroid cancer.

Treat-to-target GLP-1 agonist gradual titration schedule

Name of medication	1st dosage	28 days	1st titration	28 days	2nd titration	28 days	Final dosage
Semaglutide	0.25 mg subcutaneously once per week	→	0.5 mg subcutaneously once per week	→	1 mg subcutaneously once per week	→	1.7 mg subcutaneously once per week After four months, dosing can either stay at 1.7 mg or increase to 2.4 mg subcutaneously once per week.
Dulaglutide*	0.75 mg subcutaneously once per week	→	1.5 mg subcutaneously once per week	→	3 mg subcutaneously once per week	→	4.5 mg subcutaneously once per week.
Tirzepatide**	2.5 mg subcutaneously once per week	→	5 mg subcutaneously once per week	→	7.5 mg subcutaneously once per week	→	10 mg subcutaneously once per week Recommended maintenance dosages are 5 mg, 10 mg, or 15 mg once per week.

- To optimally utilize this treat-to-target-table, SMBG should be done fasting pre-breakfast.
- Patients should be titrated through above dosage schedules until SMBG target is attained or until the maximum recommended and tolerated dose is reached.
- *Dulaglutide is contraindicated in MEN-2, and known medullary thyroid cancer. Dulaglutide should not be recommended to patients with history of pancreatitis or those with severe GI disease, such as severe gastroparesis as this medication has not been studied in these patient populations.
- ** Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist.

Testing/diagnostics

- Test all labs initially, then repeat biomarkers every 3–6 months using clinical judgment.
- CGM for eight weeks
- BIA at baseline and monthly
- Oura Ring

Interventions

Coaching

Use coaching to promote self-efficacy in managing nutrition, movement, sleep, stress, and social relationships for lasting metabolic improvements.

Nutrition

Intervention	Guidelines/dosing
Modified Mediterranean diet	40/30/30 macronutrient ratio: 40% of total daily caloric intake from carbohydrates, 30% from proteins, and 30% from fats
Fiber	25–38 g daily
Protein	~1.6 g/kg (for weight loss while following a resistance training plan) (Carbone 2019)
Time-restricted eating/ intermittent fasting	• Aim to eat in an eight-hour window (16/8). • Eating earlier in the day is preferred; end by 6 p.m. if possible. • The alternative is a 24-hour fast once a week. • Start with 12/12, then 14/10, then 16/8.

Movement/exercise

Intervention	Guidelines
Movement daily	Walking (three hours a week)
Strength training	Weights, resistance training 2–3 times a week
Aerobic training	Higher intensity at least one day per week

Foundational supplementation

Intervention	Dosing
Protein	Start with a general dose of 10–20 g daily of plant-based or whey protein (although dosages are typically in the 20-40 g range).
Glutamine	15–30 g dose is required to leverage glutamine's beneficial metabolic effects as a GLP-1 enhancer.
Multivitamin/mineral	Dosing should be adjusted by the healthcare provider based on the individual's nutritional needs and metabolic goals, with consideration of product-specific guidelines.
EPA/DHA	2 g combined daily (adjust dose based on testing)
Soluble fiber	5–10 g daily
Vitamin D3+K2	5,000 IUs (adjust dose based on testing) plus 25–95 mcg daily (depending on dose of vitamin D)

Specialty supplements

Intervention	Dosing
Amarasate®	Supports effectiveness at lowest possible dose of GLP-1 medication by super stimulating the release of the bodies own appetite suppressing hormones (CCK, GLP-1, and PYY) giving additional support at meal times and nearing the end of the drug half-life (5–7 days) 1x125 mg once daily for two days, increasing to 2x125 mg twice daily, one hour before a main meal
Glutamine	5 g daily
Strength combination:	
MyHMB®	2,000 mg daily
Calcium	240 mg daily
Epicatechin	400 mg daily
PurpleForce®	100 mg daily
AstraGin®	50 mg daily
Senactiv®	50 mg daily

De-escalation/tapering off GLP-1 medication

GLP-1 prescription: The de-escalation of GLP-1 medications, such as semaglutide and liraglutide, can be tailored to individual patient needs by adjusting the weekly or daily dose reduction based on their current dosage. The general principle is to reduce the dose gradually over several weeks to allow the patient's body to adjust, while continuing to implement nutrition and lifestyle shifts.

Reduce max tolerated dose.

Medication de-escalation titration schedule

Medication	Current dosage	12 weeks outcome achieved (i.e., goal weight or A1C)*	Dose reduction
Semaglutide	Max tolerated dose subcutaneously once per week	→	Reduce dose in the same fashion the dose was increased over at least 12 weeks to prevent weight gain. (i.e., 2 mg → 1 mg → 0.5 mg → 0.25 mg or 2.4 mg → 1.7 mg → 1.5 mg → 0.5 mg → 0.25 mg)
Liraglutide	Max tolerated dose subcutaneously daily	→	Reduce dose by 0.6 mg every 4–12 weeks until discontinuation is achieved
Dulaglutide	Max tolerated dose subcutaneously daily	→	Reduce dose in the same fashion the dose was increased over at least 12 weeks to prevent weight gain. (i.e. 4.5 mg → 3 mg → 1.5 mg → 0.75 mg)
Tirzepatide	Max tolerated dose subcutaneously daily	→	Reduce dose by 2.5 mg every 4–12 weeks until discontinuation is achieved.

* **Note:** Once a goal weight has been achieved, a patient may need to remain on the effective dose for 6–12 months to establish a new weight set point, then consider slowly reducing the dose in the same way in which the dose was titrated up (i.e. Semaglutide 2 mg → 1 mg → 0.5 mg → 0.25 mg)

Testing/diagnostics

- Repeat baseline abnormal labs every three months.
- Recheck all baseline blood work after six months.

Interventions

Coaching

Coaching plays a critical role in empowering patients to develop self-efficacy in managing key lifestyle factors such as nutrition, movement, sleep, stress, and social relationships. Through personalized guidance, coaching supports sustainable metabolic improvements and long-term health outcomes.

Use coaching to:

- Restate the philosophy of GLP-1 as a bridge.
- Assess readiness to de-escalate.
- Establish personalized parameters for monitoring change during de-escalation, including hunger cues, mindset, and changes in weight and mood.

Nutrition

Intervention	Guidelines
Modified Mediterranean diet	40/30/30 macronutrient ratio: 40% of total daily caloric intake from carbohydrates, 30% from proteins, and 30% from fats.
Fiber	25–38 g daily
Protein	~1.6 g/kg (for weight loss while following a resistance training plan) (Carbone 2019)
Time restricted eating/ intermittent fasting	• Aim to eat in an eight-hour window (16/8). • Eating earlier in the day is preferred; end by 6 p.m. if possible. • The alternative is a 24-hour fast once a week. • Start with 12/12, then 14/10, then 16/8.

Movement/exercise

Intervention	Guidelines
Movement daily	Walking (three hours a week)
Strength training	Weights, resistance training 2–3 times a week
Aerobic training	Higher intensity at least one day per week

Foundational supplementation

Ingredient	Dosing
Protein	Start with a general dose of 10–20 g daily of plant-based or whey protein (although dosages are typically in the 20–40 g range)
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Multivitamin/mineral	Dosing should be adjusted by the healthcare provider based on the individual's nutritional needs and metabolic goals, with consideration of product-specific guidelines.
EPA/DHA	2 g combined daily (adjust dose based on testing)
Soluble fiber	5–10 g daily
Vitamin D3+K2	5,000 IUs (adjust dose based on testing) plus 25–95 mcg daily (depending on dose of vitamin D)

Foundational supplementation

Ingredient	Dosing
Amarasate®	Super stimulates the release of the bodies own appetite suppressing hormones (CCK, GLP-1, and PYY) to help sustain eating habits throughout and after taper 1x125 mg once daily, increasing to 2x125 mg twice daily, one hour before a main meal
Strength combination: MyHMB® Calcium Epicatechin PurpleForce® AstraGin® Senactiv®	 2,000 mg daily 240 mg daily 400 mg daily 100 mg daily 50 mg daily 50 mg daily

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