GLP-1 MEDICATION: AN EVIDENCE-BASED REVIEW



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Contents

Contributors	1
Abstract	3
Introduction	4
Semaglutide	7
Adverse Effects, Contraindications, Warnings and Precautions	9
Semaglutide and Body Composition	11
Semaglutide and Lifestyle Modification	12
The Fitness Professional and Wellness Coach	13
Physical Activity	13
Healthy Eating and Weight Management	15
Wellness	18
Conclusion	19
Key Takeaways	20
References	22

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Abstract

The growing prevalence of obesity among individuals is concerning due to its association with chronic diseases. While the promotion of physical activity and dietary intervention remains the initial step in the treatment of obesity, the use of pharmacologic agents to assist patients in achieving their goals can be a highly effective tool. The most recent option, has been the use of the prescribed glucagon-like peptide-1 (GLP-1) agonist class of medications. Initially researched and used for treating Type 2 Diabetes Mellitus, their popularity in the weight loss sector came from evidence obtained through trials that identified a notable decrease in overall body weight.

This evidence-based review will explore important issues related to GLP-1 medications, focusing on semaglutide. The discussion will cover semaglutide drug actions, adverse effects, contraindications, warnings, precautions, and the potential loss of body mass. The role of the fitness professional and wellness coach will be discussed along with suggested management strategies for individuals taking semaglutide medications.

Introduction

According to the World Health Organization, it is estimated that 1.9 billion adults 18 years and over are overweight (BMI \ge 25 kg/m²) or obese (BMI \ge 30 kg/m²). Over 340 million youths aged 5 to 19 years and 41 million under age 5 years were overweight or obese in 2016 (World Health Organization, 2021). In the United States (U.S.), data collected from 2017 to 2020 revealed that 41.9% of adults and 19.7% of youths were obese (Trust for America's Health, 2022). The estimated annual medical costs related to obesity in the U.S. were nearly \$173 billion in 2019 (Centers for Disease Control and Prevention, 2022).

Obesity can be multifactorial, which can make it a challenge to manage. Factors related to obesity may include but are not limited to behavioral (lifestyle, eating habits, regular exercise, and sleep), psychological (stress and mental health), genetic, comorbid conditions (e.g., metabolic syndrome), medications (e.g., antidepressants), environment (e.g., family influences, marital status, and social support), and socioeconomic (e.g., education and income status) (Anekwe et al., 2020, Chatterjee et al., 2020, National Institute of Health, 2023).

The growing prevalence of obesity is concerning due to its association with chronic diseases (Keramat et al., 2021). Center of Disease Control reporting of the top 10 causes of mortality in the U.S. indicates that heart disease, cancer, stroke, and diabetes accounted for 47% of all deaths in 2020 (Centers for Disease Control and Prevention, 2023). This is significant as these causes have evidence supporting dietary intervention, exercise, and lifestyle as a means of primary prevention. Simon et al. (2019) investigated means of intervention against the rise of nonalcoholic fatty liver disease (NAFLD) due to it becoming a leading cause of cirrhosis and the development of hepatocellular carcinoma and cirrhosis-related mortality. Their findings strongly suggested that the establishment of weight management and exercise could potentially prevent over 30,000 liverrelated deaths in the U.S. each year (Simon et al., 2019). These examples are but a few elevating the significance of weight management as a keystone to preventing debilitating diseases.

Given the scope of the issue and the importance of finding viable prevention and treatment options, healthcare professionals are constantly working to find ways to slow or reverse this trend. While the promotion of physical activity and dietary intervention remains the initial step in the treatment of obesity, the use of pharmacologic agents to assist patients in achieving their goals can be a highly effective tool. The United States Food and Drug Administration (FDA) approval of medications have been limited, with the majority having a narrow scope of action along with a variable degree of tolerance and unwanted side effects. The most recent option has been the use of the Incretin agonist class of medications (Food and Drug Administration, 2023).

Incretins, such as glucagon-like peptide-1, are peptides that modulate glucose metabolism by facilitating the pancreas to release insulin to reduce blood glucose levels (Müller et al., 2019). Initially researched and used for the treatment of Type 2 Diabetes Mellitus (T2DM), their popularity in the sector of weight reduction came from evidence obtained through trials, which identified

a notable decrease in overall bodyweight (Wilding et al., 2021a). The popularity of the prescribed glucagon-like peptide-1 (GLP-1) agonists has recently increased among individuals seeking weight loss (Bergmann et al., 2023). In 2005, GLP-1 medications were created to help individuals with Type 2 Diabetes Mellitus (T2DM) (Amaro et al., 2022; Latif et al., 2023). In the initial trials designed to explore the safety and efficacy of these drugs for glucose control, they also showed weight loss effects in the initial phase 2 and phase 3 trials. This led to the development of these drugs as weight-loss agents in addition to their utilization as glucose-lowering agents for people with diabetes (Amaro et al., 2022). To date, there are seven GLP-1 medications approved for T2DM: dulaglutide (brand: Trulicity®), tirzepatide (brand: Mounjaro®), exenatide (brand: Bayetta®), exenatide extendedrelease (brand: Bydureon BCise®), lixisenatide (brand: Adlyxin®), semaglutide (brand: Ozempic®, Wegovy®, Rybelsus®) and liraglutide (brand: Saxenda® and Victoza®). Two medications are currently approved for weight loss: semaglutide and liraglutide (Latif et al., 2023).

For weight loss, the most frequently prescribed GLP-1 medication is semaglutide (brand: Ozempic®, Wegovy®, or Rybelsus®), as it is approved for non-diabetic individuals who have a BMI of 27 or greater and at least one weightrelated condition (e.g., hypertension or high cholesterol) or have a BMI greater than 30 (Food and Drug Administration, 2021; Wilding et al., 2021a). Recently, semaglutide has been prescribed to individuals of all health levels seeking cosmetic weight loss (Han et al., 2023). The widespread use of semaglutide has created some concerns among healthcare professionals. The medication may help individuals temporarily lose weight but may not be ideal as a standalone treatment without adding a healthy lifestyle due to the potential of regaining weight after stopping the medication (Wilding et al., 2022) (Figure 1). There is also a

concern regarding the potentially large amount of body mass lost from semaglutide, which may include lean muscle and bone mineral density, which are important for long-term health (Ida et al., 2021; Papageorgiou et al., 2019). These negative effects appear to be analogous to those often seen in extreme or crash diets, where individuals severely reduce their energy intake and fail to maintain adequate protein intake and other key macro and micronutrients (Joshi & Mohan, 2018; Tahreem et al., 2022). Extreme dieting behaviors result in rapid weight loss, potential loss of lean muscle, and risk for frailty as the person ages. Researchers have documented that a weight loss of \geq 5% among individuals 60 years and older was a significant risk factor for frailty, and weight loss over a lifespan was strongly associated with frailty (Crow et al., 2020). Frailty has been linked to falls, fractures, and mortality among adults 75 years and older. Researchers have documented that the annual incidence rate per 1,000 older adults for falls was 10.98, fractures 18.81, and mortality 55.82 (Middleton et al., 2022). These data clearly show the potential health and safety risks related to semaglutide and extreme dieting in the absence of a supervised lifestyle program.





While clinical data suggests that rapid and substantial weight loss occurs due to the GLP-1 medication, the use may result in large portions of the body weight coming from lean body mass (Ida et al., 2021). This may increase the risk of frailty among some populations (Crow et al., 2020). Adequate protein intake may offset this loss. The recommended daily allowance (RDA) for protein intake is 0.8 g/kg/body weight to maintain nitrogen balance, while the optimal protein intake for exercising individuals is 1.4 to 2.0 g/kg of body weight (Kerksick et al., 2018). The addition of resistance training may also prove to be an effective tool for lowering the risk of lean body mass loss due to the substantial weight loss from GLP-1 utilization (Papageorgiou et al., 2019).

Combining semaglutide with a healthy lifestyle approach that includes physical activity, healthy eating, weight management, and wellness may be the best strategy for long-term weight reduction and overall health (Amaro et al., 2022; Fiorilli et al., 2022). Fitness professionals and wellness coaches are uniquely qualified to provide healthy lifestyle coaching to individuals on semaglutide. These professionals need to have a working knowledge of the medication to safely design physical activity and healthy lifestyle programs for their clients. Furthermore, healthcare professionals should be aware of healthy lifestyle strategies to safely guide their patients on the medication (Kyrillos et al., 2022).

This document will explore important issues related to GLP-1 medications with a focus on semaglutide. The discussion will cover semaglutide drug actions, adverse effects, contraindications, warnings, precautions, and the potential loss of body mass. The role of the fitness professional and wellness coach will be discussed along with suggested management strategies for these individuals.

Semaglutide

Semaglutide belongs to a class of glucagon-like peptide-1 (GLP-1) medications originally created to treat individuals with T2DM. The U.S. FDA approved once-weekly subcutaneous administration in December 2017, and once-daily oral was approved in September 2019 (Food and Drug Administration, 2021). In 2018, researchers representing the manufacturer began a planned series of 15 clinical trials called the Semaglutide Treatment Effects in People with Obesity or STEP studies, which explore the utility of the once-weekly 2.4 mg semaglutide injection among individuals with overweight and obesity with or without T2DM (Alabduljabbar et al., 2022). In 2019, researchers also began studying the effects of semaglutide among adolescents 12 to 17 years of age as part of the STEP TEENS clinical trial (Weghuber et al., 2022). In 2021, semaglutide (brand: Wegovy) was approved by the FDA to treat overweight and obesity (BMI \geq 27 kg/m²) in non-diabetic individuals 12 years of age or older (Food and Drug Administration, 2021). Other forms of semaglutide (brand name: Ozempic and Rybelsus) may be prescribed "off-label" by medical doctors for weight loss among non-diabetic individuals (Han et al., 2023). To date, seven of the STEP studies have been published (Alabduljabbar et al., 2022; Novo Nordisk, 2023).

Semaglutide is a modified polypeptide molecule that mimics the endogenously produced glucagonlike peptide-1 (GLP-1) hormone. Native GLP-1 is an incretin class hormone, which is a glucosedependent insulin secretagogue. Discovery of this class was significant in treating T2DM as it improved insulin release and beta-cell activity while minimizing the risk of negative effects of hypoglycemia (Tan et al., 2022). Native GLP-1 is produced in the enteroendocrine L-type cells, with the highest population found in the distal small intestine. Receptors on the apical side of the L-cells respond to post-prandial mono- and polysaccharides along with protein and lipids, stimulating basal receptors post-absorption. The result of GLP-1 production and release stimulates GLP-1 receptors found in numerous locations throughout the body, including but not limited to the stomach, pancreas, adipose tissue, vascular smooth muscle, myocardial cells, and the brain (Gribble & Reiman, 2021). Further research has brought to light the impact of GLP-1 on the brain, noting receptors in the nucleus tractus solitarius of the caudal brainstem and the POMC neurons with the Arcuate nucleus of the hypothalamus (Kanoski et al., 2016). This is highly significant as not only

is this the initial stimulation of vagal signaling from the gut to the brain, but it is also a key area that regulates energy homeostasis and satiety. In addition, a local GLP-1 hormone has now been found to be produced within the brain and may affect learning of sensory associations (Hanssen et al., 2023). The results of GLP-1 receptor stimulation at these various sites have been the keystone to their impact on weight reduction, with stimulation resulting in slowing of gastric emptying in the stomach, thereby increasing satiety, stabilizing of adipose tissue, which minimizes improper triacylglycerol breakdown, improving appropriate insulin and glucagon release from the pancreas, and blunting food-seeking behavior at the level of the brain to name a few (Tan et al., 2022; Defronzo, 2009). However, a significant limiting factor of native GLP-1 hormone is the short half-life of 2 to 3 minutes. This quick denaturation limits the ability to reach serum levels, which promotes weight loss by modification of the peptide molecule that allows for long-sustained activity. Such is the case with semaglutide, which can maintain activity with a once-a-week administration (Meier, 2021). The current body of research does suggest that the GLP-1 medications may have a larger effect

SEMAGLUTIDE

on the body by reducing cardiometabolic risk factors (e.g., high blood pressure), improving renal function (e.g., reducing albuminuria), and weight loss (Latif et al., 2023). It is important to note that the medication-related physiological effects may differ among individuals, resulting in varied results (Bergmann et al., 2023). It is also important to consider that different GLP-1 medications may have varying effects on individuals, including their lean body mass.

Lower doses of semaglutide, as low as 0.25 mg once weekly, are sufficient to show glycemic benefits, whereas higher levels of semaglutide (e.g., 2.4 mg once weekly injection) have been shown in the research to significantly reduce body weight among individuals due to the interaction with the gut and brain, leading to early satiety and reduction in food-seeking behavior (Blüher et al., 2023; Gao et al., 2022). Patients may see a reduction of body weight and improved glucose control even at minimum doses. Titrating up is based on individuals' tolerance and noted benefits. It is critical to emphasize that the trials that have demonstrated a significant reduction in body weight were designed to incorporate exercise prescription and dietary modification with scheduled followups. This is documented in the semaglutide STEP 1 trial (Wilding et al., 2021a). Participants who received semaglutide and lifestyle intervention for 68 weeks lost a mean of 14.9% of baseline body weight versus participants in the placebo group who lost a mean of 2.4% body weight (Wilding et al., 2021a). Participants also adhered to a reducedcalorie diet (500-kcal deficit per day) as part of the lifestyle modification, which may have contributed to the weight loss (Wilding et al., 2021ab). It is important to note that researchers did not compare the medication only to the medication + lifestyle intervention. However, a study looking into the effects of Liraglutide (the first GLP-1 approved for weight-loss) and its ability to reduce both body weight and body-fat percentage loss as two

independent outcomes and the role of exercise may have provided important insight (Lundgren et al., 2021). Participants went through an 8-week calorie-reduced portion, which was proceeded with a 52-week trial placing participants in a four-group parallel format that investigated the final amount of overall body weight and specifically body-fat lost with groups separated into placebo with no exercise prescription, exercise prescription alone, liraglutide alone, and exercise with liraglutide. When comparing the liraglutide without exercise and exercise without liraglutide, we note that the group that received liraglutide alone lost more overall body weight than the exercise group, but the group with exercise alone lost more body fat than the liraglutide group. This is very significant as it highlights the importance of monitoring body composition while patients are utilizing these agents and the role of exercise in promoting body fat loss (Lundgren et al. 2021). Due to the potential loss of appetite, individuals may consume lower amounts of calories, requiring them to increase protein intake to help attenuate the loss of lean muscle (Ogilvie et al., 2022). This may be challenging due to protein's satiety effects, which can be mitigated by consuming a protein shake. The GLP-1 medication may produce favorable weight loss results among individuals who respond to the treatment. However, some individuals may not respond well to the medication due to possible adverse effects discussed in the following section (Amaro et al., 2022).

GETTING TECHNICAL

Professionals should consider that the STEP clinical trials included the addition of a lifestyle intervention, which was an important part of the treatment. The lifestyle intervention among all studies included the following (Alabduljabbar et al., 2022; Wilding et al., 2022):

- 1. Counseling and Behavior Therapy: Participants received counseling sessions (every 4 weeks) to help them adhere to a reduced-calorie diet (500-kcal deficit per day) and increased physical activity (150 minutes per week of physical activity). *Note:* The Step III trial included greater physical activity (up to 200 minutes per week) and intensive behavior therapy that included 30 counseling sessions with a registered dietitian over 68 weeks covering topics such as dietary changes, physical activities, and behavioral strategies to ensure the appropriate implementation and compliance with the intervention (Wadden et al., 2021).
- **2.** Activity Tracking: Both diet and activity were recorded daily in a diary or using a smartphone application or other tools and reviewed during counseling sessions.

The results from the STEP clinical trials support the addition of a multimodal lifestyle intervention that may include counseling, physical activity, and activity tracking. Lifestyle programming should be unique for each client. Some clients may respond well to a standard lifestyle program or may need more intensive exercise and behavior counseling, as documented in the STEP III trial. It is important to note that the STEP trials were vague in their reporting of which modes of physical activity participants performed during the studies. It is recommended that individuals conduct a combination of aerobic and anaerobic exercise. These guidelines will be discussed in the upcoming section.

Adverse Effects, Contraindications, Warnings, and Precautions

Semaglutide has several adverse effects reported by the manufacturer (Novo Nordisk, 2023). Common adverse effects include but are not limited to stomach issues (nausea, vomiting, abdominal pain, or distention), gastrointestinal issues (diarrhea, constipation, or flatulence), fatigue, dizziness, runny nose, sore throat, and headache (Novo Nordisk, 2023; Stottlemyer et al., 2023). Researchers analyzed pooled data from the Semaglutide Step 1–3 trials (N = 2117) and found that stomach and G.I.-related adverse effects were more common with Semaglutide 2.4 mg versus the placebo. They documented that nausea (43.9% vs. 16.1% of participants), diarrhea (29.7% vs. 15.9%), vomiting (24.5% vs. 6.3%), and constipation (24.2% vs. 11.1%) were commonly found among participants (Wharton et al., 2022). Other reported adverse effects include vision changes, allergic reactions, increased heart rate, depression, and suicidal thoughts (Novo Nordisk, 2023).

SEMAGLUTIDE

The semaglutide manufacturer recommends that individuals with a personal or family history of medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2 (MEN2), or individuals with a hypersensitive reaction to semaglutide avoid taking the medication (Novo Nordisk, 2023). They are considered contraindications. Other warnings and precautions when taking semaglutide include but are not limited to pancreatitis, gallbladder disease, kidney injury, diabetic retinopathy complications, and possibly thyroid c-cell tumors (Novo Nordisk, 2023; Smits & Van Raalte, 2021).

The fitness professional and wellness coach should have a basic understanding of common adverse reactions, contraindications, warnings, and precautions. These noted issues are not allinclusive; individuals may respond differently to the medication. Fitness professionals and wellness coaches may need to carefully monitor the individuals taking semaglutide while participating in an exercise and healthy lifestyle program to ensure their safety. The individual's prescribing healthcare professional (e.g., MD) should be consulted if there are any questions regarding client safety, or the individual should be referred to their healthcare provider if any complications from the medication are suspected. The professional can also consult a registered dietitian (RD) if more nutritional counseling is needed.

Fitness professionals and wellness coaches should also be aware of individuals taking compound or counterfeit GLP-1 medications or GLP-1-like medications, as they may be unsafe (Novo Nordisk, 2023). As of May 2023, Ozempic® and Wegovy® are in shortage in the U.S., allowing them to be compounded (Food and Drug Administration, 2023). Compounding medications can cost considerably less than the brand-name product. However, the FDA recently reported adverse events from individuals taking compounded semaglutide. They also noted that some compounders use a salt form of semaglutide, which may not contain the same active ingredients as the FDA-approved product (Food and Drug Administration, 2023). To date, the semaglutide sodium and semaglutide acetate salt forms have not met the FDA safety requirements. Compounded medication with these ingredients may be unsafe for individuals (Food and Drug Administration, 2023). Additionally, these compounded formulas lead to potential inaccuracy in dosage. A higher dosage than what is described to the patient increased their risk for adverse reactions identified above. Also, some individuals purchase semaglutide peptides (sold for "research use") from unregulated and unlicensed sources to make their own medication. These peptides may be unsafe as they may not have undergone appropriate safety testing and FDA approval (Food and Drug Administration, 2023). This is very concerning as these medications cross the blood-brain barrier, which opens the patient to unexpected risks when possible contaminants are present. Lastly, the semaglutide manufacturer and the FDA reported on June 16th, 2023, discovering counterfeit Ozempic® (semaglutide injection) in the U.S. The counterfeit product contained another diabetic medication called insulin glargine injection, which works differently than semaglutide, which can lead to an adverse event (Novo Nordisk, 2023). Medication purchased online or in-person by foreign or unlicensed sources may be misbranded, adulterated, counterfeit, contaminated, improperly stored, transported, ineffective, and/or unsafe (Novo Nordisk, 2023). The fitness professional and wellness coach should refer individuals to their healthcare provider if their client purchased and/ or received the medication from an unregulated, unlicensed source or if they suspect the medication is counterfeit. Counterfeit medications could be a serious health risk for individuals. The manufacturer has a webpage dedication to this topic (https://www. novonordisk-us.com/media/news-archive/news-details. html?id=166119).

FOOD FOR THOUGHT

Researchers and the manufacturer of semaglutide have documented several adverse effects, but these effects are not limited to stomach issues, gastrointestinal issues, fatigue, dizziness, runny nose, sore throat, and headache (Novo Nordisk, 2023; Stottlemyer et al., 2023). It is important for the professional to consider that these adverse effects may have multifactorial causes, such as the medication, individual dietary patterns, and consuming multiple medications that may magnify the adverse effects. For example, an individual with a reduced-calorie diet may experience fatigue, constipation, nausea, and diarrhea (National Institute of Diabetes and Digestive and Kidney Diseases, 2023).

Semaglutide and Body Composition

For individuals on semaglutide, there is an emerging concern among healthcare professionals regarding weight reduction and possible loss of lean muscle mass and bone density (Ida et al., 2021; Papageorgiou et al., 2019). Researchers from the STEP 1 trial conducted an exploratory body composition analysis via dual-energy X-ray absorptiometry (DEXA) on 140 non-diabetic overweight or obese participants who completed the 68-week intervention of semaglutide and lifestyle changes. Participants lost a total of 15% body weight (baseline: 98.4 kg, 68 weeks: 83.76 kg), with 40% of the lost weight coming from lean muscle mass (~5.5 kg). The total lean body mass decreased from baseline to 68 weeks was -9.7 % (baseline: 53.9%, 68 weeks: 44.2%) (Wilding et al., 2021b). Other researchers have documented modest weight loss (~12 pounds) among study participants after a 52-week intervention with semaglutide. However, ~40% of total weight loss came from lean muscle mass (McCrimmon et al., 2020).

The potential loss of lean muscle mass from semaglutide is a growing concern among healthcare professionals (Cassata, 2023). In some cases, semaglutide may not directly cause a loss of lean muscle but may mimic the longer-term effects of a very low-calorie diet (VLCD), which can result in a loss of lean muscle mass (Ardavani et al., 2021). Potential minor negative effects of a VLCD may include but are not limited to dizziness, fatigue, headache, constipation, flatulence, and feeling cold (Christensen et al., 2011; Leeds, 2014). Greater negative effects may include but are not limited to nutrient deficiencies, depression, anxiety, gout, and gallstones (Ein et al., 2019; Johansson et al., 2011; Leeds, 2014; Snel et al., 2012).

For bone density, researchers have primarily studied the efficacy of the GLP-1 medications on bone density among individuals with T2DM. The researchers found no significant association between semaglutide and loss of bone density in this population (Daniilopoulou et al., 2022; Ozeki et al., 2022).

Perhaps the basis of the growing concern is the widespread use of semaglutide by individuals of all health levels and adiposity levels seeking cosmetic weight loss. Individuals with BMIs outside of well-studied groups and with different health statuses (e.g., no metabolic disorders) may respond differently than participants from the controlled studies that underwent a supervised and structured intervention program (medication and lifestyle changes). These individuals may experience side effects without any real benefit, or they may experience rapid weight loss but may be unable to maintain the long-term benefits due to the absence of a supervised and structured lifestyle program (Wilding et al., 2022). For example, some

individuals who are obese or overweight may take the medication for weight loss without the addition of a healthy lifestyle intervention. They may be at risk of regaining weight due to the lack of personalized lifestyle coaching (Wilding et al., 2022).

Another example may be individuals who want to lose weight for non-health-related reasons, such as cosmetic appearance. The rapid weight loss could put them at risk of losing lean muscle and possibly bone density if not properly supervised by a healthcare provider. Also, semaglutide has the potential to be used by physique athletes seeking changes in body composition in preparation for competition. The fitness professional and wellness coach should consider these potential client examples and the benefits and challenges of coaching and recommending healthy lifestyle strategies.

Semaglutide and Lifestyle Modification

Several researchers have documented weight loss among individuals taking semaglutide (Amaro et al., 2022; Gao et al., 2022). Specifically, researchers representing the manufacturer have completed several of the STEP studies that have documented positive results (Alabduljabbar et al., 2022). To date, seven STEP studies have been published, which all have included semaglutide with a lifestyle intervention that included one or more of the following: dietary counseling, low-calorie diet, unsupervised weekly light- to moderate-intensity physical activity (100 to 200 min. per week), and intensive behavior therapy with registered dietitians (Alabduljabbar et al., 2022). Among the published studies, participants lost an average of 13.2% body mass over an approximate 68-week intervention period (Alabduljabbar et al., 2022).

Overall, it appears that the combined intervention of semaglutide and lifestyle modification may produce positive results among individuals seeking weight loss. However, this type of intervention may have temporary effects if the intervention is halted. Researchers from the STEP 1 study conducted a secondary analysis of 327 participants 1 year after the original study that included a 68-week intervention period. The researchers found that participants who stopped semaglutide (2.4 mg once weekly injection) and their lifestyle intervention gained back two-thirds of their prior weight loss, with regressive changes in cardiometabolic variables (e.g., blood sugar levels and blood pressure) (Wilding et al., 2022). Participants regained an average of 11.6% body weight. In a subgroup analysis, participants with greater weight loss during the 68-week intervention period tended to have higher weight gain 1 year after study completion but still maintained the greatest net weight loss since the start of the study (Wilding et al., 2022). The potential regression in weight loss and improved cardiometabolic variables can be challenging for individuals who need to stop semaglutide. To date, the STEP studies have demonstrated a 2-year efficacy of the medication among individuals (Garvey et al., 2022). Perhaps the continuation of a healthy lifestyle and proper coaching from the fitness professional and/or wellness coach could be enough to maintain the positive long-term effects achieved by the individual (Paixão et al., 2020).

CRITICAL!

Participants who stopped semaglutide and their lifestyle intervention gained back twothirds of their prior weight loss, with regressive changes in cardiometabolic health.

The Fitness Professional and Wellness Coach

There is a growing concern about the widespread use of semaglutide by individuals of all health levels seeking cosmetic weight loss. They may take semaglutide as a standalone treatment (without lifestyle modification) and then stop the medication once their weight loss goals are achieved. This may have negative consequences. For example, these individuals may respond similarly to the STEP 1 study participants who regressed 1 year after study participation (Wilding et al., 2022). Furthermore, these individuals may lose lean muscle mass while taking the medication but fail to regain the lost muscle after treatment. The fitness professional and wellness coach may play an important role in helping these individuals lose weight while maintaining lean muscle mass.

Fitness professionals and wellness coaches are uniquely qualified to work with individuals taking semaglutide medications. These individuals can be coached using a healthy lifestyle approach, including physical activity, healthy eating and weight management, and specific wellness practices (Rippe, 2018).

Physical Activity

Physical activity is one of the key factors of a healthy lifestyle program (Rippe, 2018). The U.S. Physical Activity Guidelines (PAG) recommend the following for adults (Piercy et al., 2018):

- Adults should participate in 150 to 300 minutes a week of moderate-intensity or 75 to 150 minutes a week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
- Adults should also participate in musclestrengthening activities 2 or more days a week.
- Older adults should do a combined training program of balance, muscle strengthening, and aerobic exercise.

The PAG for children and adolescents aged 6 through 17 recommends the following (Piercy et al., 2018):

 Children and adolescents should participate in 60 minutes or more of moderate to vigorous daily physical activity. Physical activity within the 60 minutes should include aerobic, muscle-strengthening, and bone-strengthening exercises. Each type of exercise should be done at least 3 days per week or more.

For individuals on semaglutide, a structured exercise program that focuses on both resistance training and cardiovascular exercise may be the best strategy for long-term weight loss results (Bond et al., 2023; Zouhal et al., 2020). Resistance training may be one of the most important physical activity components to attenuate the possible medication-related loss of lean muscle and bone density (Alabduljabbar et al., 2022; Papageorgiou et al., 2019). Researchers have documented that resistance training may prevent or attenuate the loss of lean muscle and bone density among individuals consuming reduced calorie weight loss diets (Mesinovic et al., 2021; Sardeli et al., 2018). It is well-documented by researchers that adequate muscle mass and strength are associated with long-term health and decreased mortality (Li et al., 2018; Wang et al., 2023). To date, there are no published studies that have examined the efficacy of a structured exercise program on lean muscle mass and bone density among individuals on semaglutide.

The fitness professional and wellness coach can use the PAG as an overall guide to ensure that individuals taking semaglutide medications meet the minimum amount of weekly exercise. Professionals should also consider using evidencebased guidelines when programming specific aerobic and muscle-strengthening activities for these individuals (Oppert et al., 2021). Several systematic reviews and meta-analyses have published exercise recommendations (Bellicha et al., 2021; O'Donoghue et al., 2021; Oppert et al., 2021) (Table 1). For weight loss and fat loss, researchers suggest 150 to 200 minutes of moderate-intensity (45–65% VO_{2max}, 50–65% HRR, >65–75% HR_{max}) or higher (> 65% VO_{2max}, >65% HRR, >75% HR_{max}) of aerobic activity weekly. High intensity interval training (HIIT) is also recommended for individuals who can safely participate (O'Donoghue et al., 2021; Oppert et al., 2021). For weight maintenance after weight loss, individuals are advised to participate in a higher

volume of 200 to 300 minutes a week of moderateintensity aerobic exercises (O'Donoghue et al., 2021; Oppert et al., 2021). For the preservation of lean muscle mass during weight loss, researchers suggest a moderate- (50 to 75% 1RM) to high-(75% 1RM or higher) intensity resistance training program (Bellicha et al., 2021; O'Donoghue et al., 2021). For combined exercise programs, most researchers agree that a combined exercise program of aerobic, resistance training, and caloric restriction will have the greatest impact on weight loss (Bellicha et al., 2021; O'Donoghue et al., 2021; Oppert et al., 2021). More specifically, interventions that combine high-intensity aerobic and high-load resistance training may have the most beneficial effects of decreasing body fat, increasing lean muscle mass, and reducing cardiometabolic risk factors (O'Donoghue et al., 2021). Aerobic or resistance training alone does provide benefits but is not as effective as a combined program (O'Donoghue et al., 2021; Swift et al., 2018). The fitness professional or wellness coach must perform a comprehensive assessment before the client participates in their exercise program to determine which strategy will be the best for them.

Table 1. Exercise Recommendations		
Exercise Recommendations	Exercise Programming	
Weight loss and fat loss	150 to 200 minutes of moderate-intensity (45–65% VO2max, 50–65% HRR, >65–75% HRmax) or higher (> 65% VO2max, >65% HRR, >75% HRmax) of aerobic activity weekly. High intensity interval training (HIIT) is also recommended for individuals who can safely participate.	
Weight maintenance after weight loss	200 to 300 minutes a week of moderate-intensity aerobic exercises	
Preservation of lean muscle mass during weight loss	Moderate- (50 to 75% 1RM) to high (75% 1RM or higher) intensity resistance training program	
Combined exercise programs	A combined exercise program of aerobic exercise, resistance training, and caloric restriction will have the greatest impact on weight loss.	

The fitness professional and wellness coach should also consider using an integrated (multifaceted) training approach with a focus on resistance training for these individuals. This may help attenuate possible decrements in lean muscle mass and bone density that could be experienced while on the medication. The NASM Optimum Performance Training® (OPT[™]) model may provide an effective framework as it provides a linear periodization pathway and time for the individual to safely adapt to their exercise program (Sutton, 2022). The professional can also use the FITTE-VP model (Frequency, Intensity, Time, Type, Enjoyment, Volume, and Progression) for programming the individual's aerobic exercises (Sutton, 2022). These two strategies will complement the aforementioned guidelines by providing the framework for safe exercise progression. As noted earlier, the professional may want to consult the individual's healthcare provider before their participation to obtain safe exercise recommendations.

THINGS TO KNOW!

Fitness professionals and wellness coaches should consider that it may be unrealistic for some individuals to begin exercising at the levels suggested in **Table 1**. These individuals may lack exercise experience and need time to adapt and change behavior. To meet such recommendations, this may require light exercise initially (e.g., 10- to 15-min. walking per day) with a slow exercise progression over time. Other factors, such as the individual's health status, fitness level, time availability, and self-efficacy, should be considered when providing exercise recommendations.

Healthy Eating and Weight Management

Healthy eating and weight management are other lifestyle factors that should be considered by the fitness professional and wellness coach. As documented in the semaglutide STEP 1 study, halting the combined intervention of semaglutide and lifestyle intervention led to participants regressing 1 year after study participation (Wilding et al., 2022). Semaglutide is a major factor in weight loss, but healthy eating impacts an individual's success. This is supported by the published manufacturer STEP studies that all included a healthy lifestyle intervention that provided supervision and counseling by registered dietitians (Alabduljabbar et al., 2022; Amaro et al., 2022). STEP study participants clearly had better outcomes when participating in a supervised, structured lifestyle intervention program.

The challenge for individuals taking semaglutide as a standalone treatment may be a risk for nutrition deficiencies, loss of lean muscle mass, and bone density due to the changes in appetite and food cravings (Alabduljabbar et al., 2022). A supervised, structured lifestyle program promoting healthy eating and weight management may benefit individuals during or after semaglutide treatment (Paixão et al., 2020). An optimal strategy for healthy eating and weight management may include the following components: amount of food intake, meal replacements, types of food eaten (e.g., culturally accepted), dietary strategies (e.g., Mediterranean diet), timing of meal consumption, meal cost, and setting realistic weight loss goals (Kim, 2021; Koliaki et al., 2018).

FOOD FOR THOUGHT

Individuals on GLP-1 medications may find meeting protein requirements to sustain lean body mass more difficult due to the appetite-suppressant effects of the medication. There are some strategies that can be used to help individuals meet their protein requirements more efficiently.

- **1.** Liquid forms of protein tend to be less satiating than solid forms. This means that protein shakes and other liquid forms of protein like kefir can provide higher protein content food sources while not being overly satiating.
- 2. Individuals can choose more protein-dense options. For example, if individuals are consuming cheese, they can consume hard cheeses like parmesan, which has ~30 grams per 100 grams of protein per 100 grams of cheese.
- **3.** Individuals can also be selective with protein sources like chicken, turkey, or pork loin, which have a much higher protein density than beef or fish. Other protein-rich food sources that individuals can utilize are egg whites compared to whole eggs, Greek yogurt instead of regular yogurt, or other easily exchangeable foods.
- **4.** The use of supplements such as creatine monohydrate and carbohydrate powders can help with muscle retention and maintaining good energy levels for exercise (Kerksick et al., 2018).
- **5.** A more aggressive caloric deficit may be imposed for individuals with higher baseline body fat levels, whereas slower rates of weight loss can better preserve lean mass for leaner people (Aragon et al., 2017).

Fitness professionals and wellness coaches should refer individuals to a registered dietician or healthcare provider if they identify eating patterns that may contribute to macronutrient or micronutrient deficiencies. In the U.S. population, there are documented micronutrient deficiencies. Data from the 2005 to 2016 National Health and Nutrition Examination Surveys found that 45% of the U.S. population had a Vitamin A deficiency, 46% vitamin C, 95% vitamin D, 84% vitamin E, and 15% zinc (Reider et al., 2020). Vitamin B12 deficiency may also exist in up to 5% of the U.S. population (Bird et al., 2017). Commonly documented micronutrient deficiencies worldwide include iron, folate, zinc, iodine, and vitamin A (Kiani et al., 2022). Among individuals with inadequate nutritional intake, participation in extreme dieting or very low-calorie diets may increase existing nutrient deficiencies (Malik et al., 2020). When combining lifestyle interventions with medications, there are several dietary/nutritional aspects that the fitness professional and wellness coach should consider.

The first is the level of calorie deficit that an individual should aim to hit. In an ideal scenario, individuals should seek to lose ~1 to 2 pounds of body weight per week to minimize lean mass lost during periods of weight loss. This is usually achieved by targeting a ~300- to 750-calorie per day deficit combined with increased physical activity (Kim, 2021; Kraus et al., 2019). These targets are slightly lower than many of the GLP-1 randomized trials demonstrating where reductions in daily calorie intake can exceed 1,000 kcals (Alabduljabbar et al., 2022). Modest reductions in calorie intake can lead to weight loss but also allow for the retention of lean body mass. Modest reductions also enable people to develop sustainable dietary

plans and habits that can be continued upon cessation of the medication (Kim, 2021; Kraus et al., 2019).

The second consideration is consuming adequate protein to help ensure lean mass preservation and promote satiety independent of GLP-1 medications. The optimal protein intake for exercising adults is roughly 1.4 to 2.0 g/kg of body weight (Kerksick et al., 2018). However, among individuals with higher BMIs, body weight may not be the most effective metric, and ideal body weight or lean body mass may be better. This is because protein recommendations are generally determined from studies based on lean individuals, wherein protein recommendations scale with lean body mass (Weijs & Wolfe, 2016). Additionally, protein recommendations start to become nonsensical at higher body weights (300 grams of protein for a 320-pound individual is probably excessive) and become very hard to adhere to. As such, protein recommendations for individuals looking to lose substantial body mass (10+ kg) should aim for protein recommendations closer to 1.4 g/kg of body weight based on lean mass or "ideal body weight." This will allow individuals to be more adherent to targets during and after weight loss (Kerksick et al., 2018).

The third consideration is utilizing the lower food drive period that individuals have while on GLP-1 medication to establish habits around food choices, portion sizes, and eating frequency that support their goals. The diminished appetite arising from these drugs presents a unique window for individuals to better monitor their habits, learn to determine hunger cues, and develop lifestyle strategies around their nutrition that they can rely on when the medication is stopped.

Another concern related to healthy eating and weight management is the consumption of alcohol. Alcohol consumption can stimulate the

appetite and may be a risk factor for obesity due to the high-calorie content of some types of alcohol (Golzarand et al., 2022; Yeomans, 2010). For example, a 5 fl. oz serving of red wine can average 125 calories, a 12 fl. oz serving of regular beer can average 153 calories, and a 9 fl. oz serving of a pina colada cocktail can average 490 calories (U.S. Department of Health and Human Services, 2023). The 2020–2025 Dietary Guidelines for Americans suggest that adults of legal drinking age should drink in moderation by limiting intake to two drinks or less daily for biological males and one drink or less daily for biological females (Snetselaar et al., 2021). Individuals taking GLP-1 (semaglutide) medication may develop some resistance to alcohol intake and cravings. Researchers have documented that semaglutide reduced alcohol intake and alcohol-seeking behavior in different rat studies (Aranäs et al., 2023; Chuong et al., 2023). From these results, researchers theorize that the GLP-1 medication may help reduce alcoholdrinking behaviors in overweight patients and individuals with alcohol use disorders (Aranäs et al., 2023). Human clinical trials are still needed to validate these hypotheses fully. To date, there are no reported negative interactions between GLP-1 medications and alcohol consumption (Aranäs et al., 2023). A potential precaution of combining the GLP-1 medication with alcohol is the possible hypoglycemic effects of the alcohol and the medication (Oba-Yamamoto et al., 2021). Both alcohol and the GLP-1 medication are associated with lowering blood sugars (Oba-Yamamoto et al., 2021; Ozeki et al., 2022). Thus, individuals taking the medication (especially those with T2DM) may need to consult their healthcare provider before drinking alcohol, as hypoglycemia can be a safety concern for these individuals (Amaro et al., 2022; Chuong et al., 2023).

The fitness professional and wellness coach can reinforce healthy eating and weight management through different nutritional coaching practices. With some individuals, the fitness professional and wellness coach may need to refer clients back to their healthcare provider or an RD for more prescriptive consultation. For example, if a fitness professional or wellness coach identifies that their client needs more prescriptive behavior counseling and meal planning, they may refer them to an RD. Or, if the client reports adverse reactions to the medication, they may be directed to the healthcare provider for further consultation and management.

Wellness

The fitness professional and wellness coach can also promote specific wellness practices to individuals as part of a healthy lifestyle strategy. Specific strategies that impact obesity and long-term health may include but are not limited to sleep, stress, and social support (Cooper et al., 2018; Lee et al., 2000; Tomiyama, 2019). A healthy lifestyle may consist of different dimensions of wellness (**Figure 2**).



Figure 2. Healthy Lifestyle and Related Dimensions of Wellness

Sleep deprivation is related to overweight and obesity levels and may counteract the effects of semaglutide (Tiwari et al., 2021). Researchers have documented that individuals who slept less than 7 hours per night were more likely to have a higher BMI and develop obesity. Also, sleep restriction was related to higher levels of ghrelin, inflammatory markers, salt retention, and decreased levels of leptin and insulin sensitivity (Cooper et al., 2018). Researchers have also documented that disturbed sleep patterns can lead to increased energy intake (e.g., excessive snacking) through consuming foods high in fat and carbohydrates (Papatriantafyllou et al., 2022). The fitness professional and wellness coach can encourage these individuals to try and get 7 or more hours of sleep per day, which can increase the likelihood of successful weight loss by 33% when combined with a healthy lifestyle program (Papatriantafyllou et al.)

al., 2022). Researchers have documented that proper amounts of sleep were associated with improved adherence to a behavior weight loss program (Landsbaugh Kaar et al., 2019).

Stress is also related to weight gain. Researchers associating stress with obesity suggest four key issues (Tomiyama, 2019). First, stress interferes with cognitive processes (e.g., executive function and self-regulation). Second, stress can alter behavior by triggering overeating and consuming food high in calories, sugar, and fat. Third, stress can cause physiological changes in the hypothalamic-pituitary-adrenal axis, reward processing in the brain, and possibly the gut microbiome. Fourth, stress can stimulate the production of biochemical hormones and peptides (e.g., leptin and ghrelin). Obesity stigma can also cause stress and sleep deprivation (Lee et al., 2000; Tomiyama, 2019). The fitness professional and wellness coach can be a positive influence by helping individuals manage stress through exercise and a healthy lifestyle approach (Schultchen et al., 2019).

Social support is another factor that should be considered by individuals seeking weight loss. Social support groups via an app, social media, or in-person have proven beneficial and may be an effective adjunct to a healthy lifestyle program focusing on weight loss (Loh et al., 2023; Simpson et al., 2020). The main benefit to social support groups may be accountability among individuals with the same goals, which can improve adherence (Shiyab et al., 2023). However, some individuals may not have access to an app or social media groups or receive support from their friends and family. The lack of social support can negatively affect the individual's adherence to a healthy lifestyle and weight loss programs (Kiernan et al., 2012). The fitness professional and wellness coach can help these individuals by having their own social media or in-person support groups or recommend groups that the individual can join. Social support can improve an individual's wellness, especially if they are feeling challenged with their healthy lifestyle program. The fitness professional and wellness coach can be great resources for these individuals.

Conclusion

The research has suggested that semaglutide combined with healthy lifestyle changes can positively impact an individual's weight loss efforts. Important lifestyle changes may include a reduced-calorie diet, regular exercise, and behavior modification (Alabduljabbar et al., 2022). Professionals should consider that semaglutide does have known adverse effects (e.g., stomach and gastrointestinal issues) that can affect individuals taking the medication (Novo Nordisk, 2023; Stottlemyer et al., 2023). There are also concerns regarding the widespread use of the medication, the amount of time individuals can be on the medication, and any long-term complications.

For individuals taking semaglutide for a short period, continuing a healthy lifestyle past cessation of medication may help them maintain their weight loss (Paixão et al., 2020). The fitness professional and wellness coach are uniquely qualified to guide individuals through a healthy lifestyle program that includes physical activity programming, healthy eating and weight management strategies, and suggestions for specific wellness practices.

Key Takeaways



1. Understanding Obesity:

Obesity is a global concern affecting both youth and adults. It is essential to recognize that obesity is multifactorial, influenced by genetic, environmental, psychological, and behavioral factors. Its association with chronic diseases and potential mortality underscores the importance of timely intervention.

2. Emerging Medication for Weight Loss:

In the battle against obesity, the Incretin agonist class of medications, especially the glucagon-like peptide-1 (GLP-1) class, has recently gained significant popularity.

3. Application of GLP-1 Agonists:

Designed primarily for T2DM patients or those overweight with related health complications, such as cardiometabolic issues, GLP-1 agonists offer a new avenue for weight loss.

4. Available Medications:

Currently, semaglutide and liraglutide are the two approved weight-loss medications in this category, with other types being prescribed with off-label use.

5. Medication Popularity:

Among these, semaglutide (up to 2.4 mg once weekly) has emerged as a top choice for weight loss, followed by Liraglutide.

6. Potential Side Effects:

Professionals should be informed of the potential side effects of semaglutide, which can range from gastrointestinal issues to dizziness, runny nose, sore throat, and headaches. There are other contraindications, warnings, and precautions that the professional should be aware of when working with individuals on the GLP-1 medications.

7. Consequences of Under Eating or Poor Diet:

Inadequate nutrient intake, whether from undereating or consuming a nutritionally deficient diet, can lead to several concerning side effects. Common manifestations include fatigue, hair loss, and constipation. Individuals must ensure that they consume a balanced and adequate diet to avoid these and other related health issues.

8. Safety First:

Fitness and wellness professionals must be watchful about individuals consuming counterfeit or compound GLP-1 or GLP-1-like medications as they might pose severe health risks.

9. Emerging Concerns:

The health community has expressed concerns about semaglutide leading to potential losses in lean muscle mass and bone density during weight reduction. This may be an effect related to low-calorie consumption and/or low protein intake. The inclusion of resistance training exercises can help mitigate the loss of LMB over a person's lifespan. Loss of bone mass has not been demonstrated in research studies to date when used for T2DM.

10. Combined Intervention:

An integrated approach of semaglutide and lifestyle modification seems promising for weight loss seekers. Implementing a holistic lifestyle program supervised by fitness or wellness professionals may be pivotal in ensuring the long-term benefits of such medications.

11. Optimizing Long-Term Lifestyle Changes:

Aim for a moderate calorie deficit, targeting a weight loss of 1 to 2 pounds per week while ensuring protein intake is around 1.4 g/kg based on lean mass or "ideal body weight" to maintain muscle mass. Additionally, the decreased appetite from GLP-1 medication should be seen as an opportunity to establish healthy eating habits and understand hunger cues.

12. Role of Fitness and Wellness Professionals: With their expertise, fitness professionals and wellness coaches are well-positioned to guide individual lifestyle programs to support GLP-1 medications. A well-rounded approach encompassing physical activity, a balanced diet, weight management strategies, and wellness practices can ensure optimal results for these individuals.



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