SEMAGLUTIDE AND LIFESTYLE INTERVENTIONS IN PEOPLE WITH TYPE 2 DIABETES

Jayme Limbaugh

Abstract:

Obesity continues to grow to escalating proportions, with a projected 50% of the United States population being classified as obese by the year 2039. 90% of people with type 2 diabetes (T2D) are obese. Consequently, more people with T2D are being prescribed Glucagon-like peptide 1 (GLP-1) and/or glucagon insulinotropic (GIP) medications given their efficacy for weight loss. However, there are concerns regarding the quality of weight loss, including skeletal muscle mass (SMM) loss, fat-free mass (FMM), sarcopenia, and additional adverse effects. Furthermore, studies showing weight regain to baseline after cessation of medication treatment warrant attention.

This literature review examines the complexities of the relationship between GLP-1 and body composition (FMM), SMM, weight regain after cessation, and lifestyle interventions' role in mitigating adverse outcomes. It is vital to incorporate a care team of registered dietitian nutritionists (RDN), exercise specialists, and primary care providers (PCP). This interdisciplinary team will prescribe tailored lifestyle interventions. These interventions will address personalized exercise prescriptions, comprehensive diet education emphasizing optimal macronutrient intake, weight management strategies, and blood glucose control.

Introduction:

Obesity has reached epidemic proportions, with projections suggesting that 50% of the United States (US)population will be considered obese by 2039.[1] Excess weight, particularly excess appendicular fat mass, is associated with an increased occurrence of comorbidities such as type 2 diabetes (T2D), hypertension (HTN), dyslipidemia, and cardiovascular disease (CVD).[2,3] In 2017, the Centers for Disease Control (CDC) reported that 42% of citizens in the US were living with T2D, and 90% of these citizens were classified as overweight or obese (BMI >25 kg/m2).[1] The cost of diabetes in 2017 was 327 billion dollars, with an estimated 237 billion dollars in direct medical expenses such as hospital visits, pharmaceuticals, and clinic visits.[2] Therefore, interventions such as new pharmaceutical developments leading to long-lasting weight loss and improvement in T2D management or disease remission are imperative when considering associated economic costs and reduced disease burden.

The development and use of injectables as pharmacological interventions, specifically glucagon-like peptide one agonist (GLP-1), for the treatment of diabetes have increased considerably over the last decade.[3] GLP-1 functions as an incretin gut hormone with various functions in the body, including but not limited to delaying gastric emptying, increasing satiation, boosting insulin secretion, promoting diuresis, and reducing inflammation.[3] It has been theorized that increased circulation of GLP-1 would benefit individuals seeking weight loss as a form of management for T2D.[3] However, the peptide GLP-1 naturally produced by the body has a short

half-life of 1.5-5 minutes. [4] Therefore, pharmaceutical companies developed GLP-1 mimetics with a longer half-life (13-336 hours) to aid weight loss in individuals with T2D and those who are overweight or obese.[4] The first GLP-1 brought to market as an approved treatment for T2D in 2005 was exenatide; followed by liraglutide (2010), albiglutide (2014), dulaglutide (2014), lixisenatide (2016), beinaglutide (2016) , semaglutide (2017), PEG-loxenatide (2019), and tirzepatide (2022).[4]

Wantanabe et al. studied prescription increases throughout 2014 to 2022 in prescribed GLP-1's as they became available with reporting as follows: 83.9% for semaglutide-1, 119.2% for semaglutide-2, 84.8% for semaglutide-3, 53.3% for liraglutide, 12.9% for lixisenatide, 78.8% for dulaglutide, and 254.3% for tirazepitide.[3] The highest increases were seen in semaglutides. Semaglutides have documented long-term weight loss and improved cardiovascular issues, such as reduced total cholesterol and triglycerides.[5] Despite the documented benefits of GLP-1 therapy, concerns have arisen regarding its impact on body composition, metabolism, and the effects of therapy cessation.[6] Therefore, this review aims to provide background on the mechanisms of weight loss for people with T2D to inform clinicians in primary care settings about the benefits and risks involved for patients with GLP-1 therapy.

Impact of weight loss on metabolism and skeletal muscle mass

A physiological adaptation associated with weight loss involves resting energy expenditure (REE) or basal metabolic rate (BMR) changes.[7] REE is the energy required to maintain physiologic functioning and is responsible for 60-70% of total energy expenditure.[7] BMR is the total calories burned at rest from all physiological influences.[7] Body composition, specifically skeletal muscle mass (SMM), influences REE heavily. [8] Therefore, if a reduction in SMM

accompanies a weight reduction, there will be a subsequent reduction in REE and BMR.[8] This raises concern about the long-term side effects of weight loss while on a GLP-1 if accompanied by a reduction in SMM and decreased REE and RMR. Loss of appendicular skeletal muscle mass (ASMM) in men 50 or greater years of age had a more significant relationship with mortality.[9] In the Szulc et al. study, men aged 50 and over who had significant rapid loss in appendicular skeletal muscle mass (ASMM) had a strong predictor of mortality (3.60; 99% CI: 1.64, 7.89).[9]

Discontinuation of Treatment and Weight Regain

As more private insurance payers no longer cover GLP-1 for patients desiring weight loss or patients with diabetes who are meeting their weight and lab goals are opting to discontinue treatment. There is limited research examining the effects of discontinuation of GLP-1 treatment and the "rebound" effects in persons with or without diabetes. The SURPASS-1 study examined the implementation and dosage effects of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) medication, tirzepatide, in people with diabetes who were not engaging in diet or exercise programming for three months before initiation of the study.[10] The SURPASS-J Mono study, an extension of the primary SURPASS-1 study, followed nine subjects from the SURPASS-1 study with diabetes 52 weeks after cessation of tirazepatide.[11] The participants were five males and four females, with an average age, hemoglobin A1C (Hgb A1C), and body mass index (BMI) of 54.3 +/- 5.4 years, 7.9% +/-0.3%, 33.5 +/-3.3 kg/$m^{2,}$ respectively. Subjects were randomly assigned to group of 5mg, 10mg, or 15 mg of tirzepatide or 0.75 mg of dulaglutide.[11] After 52 weeks of treatment, participants in the tirzepatide 5 mg group had an average body weight change of -6.5 +/-1.9kg (6.0% loss), -7.3kg (7.0 loss) in the 10 mg group,

and a -11.4+/-0.2kg (16.8% loss) in 15 mg group. However, the dulaglutide 0.75mg group gained +0.2 kg (0.3% increase). After discontinuation of the drug at 52 weeks, weight regain was measured at two-, four- and six-month intervals. The 5 mg weight changes were +2.1kg (2.2%), +3.2kg (3.2%), and +3.6kg (3.6%) for the 5mg tirzepatide dosage +5.8 kg (6.0%), +6.3 kg (6.4%), and +6.0 kg (6.2%) for 10 mg dosage; +7.7 kg (13.9%), +9.4 kg (17.0%) and +10.1 kg (18.0%) for 15 mg dosage; 2.9 kg (4.0%), 2.3 kg (3.2%), and +3.6 kg (5.0%) in 0.75 mg dulaglutide dosage group.[11]

The STEP 1 trial extension studied weight regain and its influence on cardiometabolic health upon cessation of a semaglutide in participants without diabetes.[10] The study included 1961 participants with an average age of 48 +/- 12 years and a body mass index (BMI) greater than or equal to 30 kg/m2 with one or more comorbidities related to increased weight. Comorbidities were described as HTN, dyslipidemia, obstructive sleep apnea (OSA), or CVD. None of the participants had diabetes mellitus.[6] Participants were randomized to receive a semaglutide or placebo initiated at 0.25mg/week, and the dosage was increased every four weeks until the target dose of 2.4 mg/week. The entire study was conducted over 68 weeks. Lifestyle and physical activity were also addressed during the intervention. Lifestyle counseling was performed every four weeks with a goal of a reduction in 500 kilocalories per day relative to total energy expenditure. Physical activity was set at 150 minutes per week. At the end of 68 weeks, 327 subjects were randomized to stop all treatment, including physical activity and nutrition counseling. The subjects were followed up with data collection for an additional seven weeks.[6]

Participants randomized to the intervention group lost an average of 17.3% body weight from baseline over the first 68 weeks of the study. [12] The same participant group 120 weeks after cessation of treatment regained baseline weight plus an additional average of 5.6%. [10] As anticipated, cardiometabolic factors improved concurrently with weight loss in the GLP-1 group. However, after treatment withdrawal, systolic and diastolic blood pressure returned to baseline by week 120. C-reactive protein (CRP), high-density lipoprotein (HDL), cholesterol, very low-density lipoprotein (VLDL), triglycerides, and lipids also increased after cessation of treatment but remained overall improved compared to baseline.

Clinical Application

While the GLP-1 has been shown to support weight loss success and decreased cardiovascular risks, consideration must be given to the potential downsides. People with diabetes would benefit from lifestyle interventions from a multidisciplinary team such as PCPs, RDNs, and exercise specialists.

In a primary care setting, clinicians would benefit from implementing baseline testing for SKM and FFM for patients prescribed a GLP-1 as a form of diabetes treatment. -Air displacement plethysmography (ADP), bioelectrical impedance analysis (BIA), and dual x-ray absorptiometry (DXA) are more commonly utilized methods of indirect body composition.[7] While ADP is the preferred clinical form of measurement due to its high accuracy and low cost, it is not readily found outside research settings and requires a trained technician to ensure high accuracy. [7]

DXA is available in some clinical outpatient settings; however, its widespread application is limited by expense and lack of portability. BIA is easily accessible and affordable, and it has accurate readings. Still, education will need to be provided to the patient regarding adherence to pre-measurement guidelines to ensure accuracy, such as the patient's hydration status, which can be influenced by exercise, dehydration, or ambient temperature.[7]

The American College of Sports Medicine recommends cardiorespiratory exercise for people with T2D three to seven days per week with no more than two consecutive days. The intensity should be moderate to vigorous, depending on the individual.[7] The recommended time is 150 minutes per week of moderate intensity with 75-150 minutes per week for vigorous or a combination of moderate and vigorous intensity.[7] Types of exercises recommended for increased physical activity depend upon the individual's starting baseline functional state. Exercises suggested, but not limited to, are walking, jogging, cycling, rowing, and weight training.[7] Specific resistance exercise recommendations to maintain or increase SMM are at least two days per week, preferably three days, of nonconsecutive moderate to vigorous strength exercises of 8-15 repetitions.[7] The exercise programming should be prescribed by a certified exercise physiologist or exercise specialist to reduce the possibility of injury.

In addition to increased physical activity, the PCP should refer to an RD for specific nutritional guidance. Goals should be focused on preserving SMM and promoting weight management to help reduce the metabolic issues discussed: reduced BMR and weight regain after GLP-1 and/or GIP cessation. Education regarding total calorie intake, protein, fluid, and blood glucose control should always be individualized to the specific patient. However, generic protein

recommendations for building or maintaining SMM are 1.6-1.7 grams per kilogram of body weight per day. [13] Fluid intake recommendations are 25-35 mL/kg, depending on age and exercise output.[14] According to the Institute of Medicine (IOM), fat recommendations are 20-35% of the recommended daily caloric intake. [14] Carbohydrate recommendations and blood sugar management should be addressed by the RDN and included in the plan of care for patients with diabetes, as this can vary between patients and their medications, blood weight, activity levels, etc.[7]

Conclusion

Including cardiorespiratory and resistance exercise, in addition to nutrition intervention can effectively manage the previously mentioned metabolic and musculoskeletal side effects of weight loss, especially rapid weight loss associated with T2D patients being prescribed a GLP-1 and/or GIP medication. A decrease in SKM or FFM is theorized to be a result of poor glycemic control and subsequent decline in physical activity and exercise, which is correlated with an increase in slips, trips, falls, hospitalizations resulting in a decrease in activities of daily living, and lower quality of life.[9] Prescribed GLP-1 for better glycemic control has been associated with overall weight loss, with research observing this as rapid weight loss.[9] However, more research is needed on the quality of weight loss, specifically FFM and SMM. Furthermore, more research is required to examine the influence of pharmaceutical interventions and lifestyle changes, such as referrals to RDNs and exercise specialists. Therefore, a care team incorporating RDNs is imperative to achieve the success of GLP-1 in patients with diabetes. The goals of this partnership are to support weight loss and better glycemic control while being

mindful of the nutritional needs and possible side effects of people with diabetes who are prescribed a GLP-1.

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