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Maintaining Fat-Free Mass and Muscle Mass during obesity therapy with Incretin-Mimetic Drugs

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ABSTRACT

Introduction

Obesity is one of the major public health challenges of the 21st century. In recent years, incretin mimetic drugs (IMDs), primarily liraglutide, semaglutide, and tirzepatide, have gained popularity due to their ability to help patients lose 10%-20% of their body weight. However, it has been observed that during treatment with these medications, patients also lose fat-free mass (FFM) and muscle mass (MM), which is one of the main negative side effects.

Available scientific knowledge provides limited information regarding preventing FFM and MM loss associated with IMDs treatment of excess body weight.

Aim of the study:

This study aims to analyze current information about strategies that minimize the loss of FFM and MM and muscle function and consider using methods to prevent muscle atrophy in patients treated for obesity with other methods, such as diet, exercise, and bariatric surgery, to form a holistic approach for patients treated with IMDs.

Materials and Methods

This review was conducted by searching scientific publications on PubMed, Google Scholar, and Clinicaltrials.gov databases. The analysis included articles concerning FFM and MM loss in the most common obesity treatment therapies and articles that provided information about the impact of exercise and nutrition combined with IMDs in obesity treatment and proper weight maintenance. Subsequently, a succinct summary of the gathered data was provided.

Conclusion

The research findings indicate that two primary factors significantly influence the preservation of FFM and muscle mass MM during weight loss therapy: proper nutrition and physical activity. During weight loss interventions, diets should consist of adequate high-quality protein, which contributes to reducing MM loss. Furthermore, physical activity, particularly resistance training, demonstrates a markedly positive effect on the maintenance of MM. Research results reveal that patients treated with Incretin-Mimetic Drugs (IMDs) who engage in physical exercise sustain their reduced body weight more effectively than those who rely solely on IMDs. All patients undergoing obesity treatment with IMDs must participate in comprehensive programs that offer an appropriate dietary regimen and individually tailored physical exercise plans. By integrating medication with lifestyle interventions, patients can optimize the benefits of IMD treatment while mitigating potential adverse effects on FFM, MM, and overall health.

Keywords: Obesity, overweight, GLP-1 agonists, Fat-Free Mass, Lean Body Mass, Muscle Mass, Obesity treatment, exercise, protein intake.

Introduction

Obesity and overweight are one of the most significant public health challenges of the 21st century. The number of people with excessive body weight has more than doubled since 1990, and in 2022, 1 in 8 people in the world was obese(1). In Poland, as of 2019, 20% of male and 18% of female adults had a BMI over 30kg/m², and over the next 30 years, Poland will lose approximately PLN 108 billion (4.1% of GDP) due to obesity-related diseases, an average of approximately PLN 3.6 billion per year (approximately 0.14% of GDP) (2). As a complex chronic disease, obesity affects health, increases the risk of long-term medical complications, and reduces the quality and length of life(3).

Treatment of obesity is gaining more and more attention due to the increasing number of people with excess body weight and the growing number of methods of therapy (4,5). The pharmacological approach to fight obesity with Incretin-Mimetic Drugs (IMDs) such as glucagon-like peptide 1 (GLP-1) receptor agonists semaglutide and liraglutide and GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor co-agonists tirzepatide has gained enormous importance in recent years, especially because these agents have shown to elicit weight reductions of up to 15-20% and such efficacy was previously only available with bariatric surgery (6,7).

However, clinical studies demonstrating the remarkable effectiveness of this new treatment have shown that FFM is also lost in addition to Fat Mass (FM), which is one of the main concerns in the treatment of obesity by IMDs (6,7). MM and internal organ tissues have a higher metabolism rate, which helps maintain a healthy body weight after the therapy. Correct MM and muscle function are also important factors in physical performance, quality of life, and metabolic health (8). The Global Leadership Initiative on Malnutrition also recognized reduced MM as a criterion for diagnosing malnutrition(9). Therefore, there is a need to search for optimal methods that maximize body FM reduction while minimizing the loss of FFM, especially MM, during therapy of obesity with IMDs.

How do Incretin-mimetic drugs work?

GLP-1 receptor agonists are used for type 2 diabetes (T2DM) treatment due to their influence on increased glucose-dependent insulin secretion, decreased glucagon secretion, and delayed gastric emptying. (10) Reduction of food intake and body weight loss have also led to their use in treating obesity. The main mechanism influencing weight loss is the reduction of

calorie intake. The proposed mechanism for increased energy expenditure at rest in mice and rats has not been confirmed in humans(11,12). Treatment of obesity with semaglutide once per week for 12 weeks reduced food intake by 24% without any change in resting energy expenditure. (13) Gastric distension and peripheral vagal nerve activation enhance insulin secretion, inhibit glucagon secretion, and slow down stomach emptying, helping to reduce weight during treatment with GLP-1 receptor agonists. Still, besides that, GLP-1 receptor agonists induce satiety by influencing brain regions involved in the regulation of feeding. There is a widespread presence of GLP-1 receptors within the Central Nervous System (CNS), and studies show that they participate in feeding regulation by endogenous GLP-1 receptor agonists (14,15). Exogenous GLP-1 receptor agonists vs. placebo showed decreased food-related brain responses in T2DM patients and obese subjects (in the insula, amygdala, putamen, and orbitofrontal cortex) on food pictures measured by function MRI. GLP-1 receptor activation modulates appetite- and reward-related brain areas in obese and T2DM subjects, correlating with reduced food intake (16). The widespread of GLP-1 receptors in the CNS and the different effects of activation of different populations of these receptors explain the differences in the effects of various drugs in this group. Therefore, targeting the appropriate population of GLP-1 receptors may enable better weight loss and reduce the most common negative side effects(17). The emergence of a GLP-1 receptor and GIP receptor co-analog - tirzepatide - and even better effects on body weight loss than previous GLP-1 receptor agonists (18) make us consider how the GIP receptor activation helps people lose weight. The GIP receptors are present in multiple areas of mice and the human brain in neurons and glial cells. There are also parts of the CNS, like the hypothalamic and hindbrain, where there is co-expression of GIP and GLP-1 receptors, and activation of both may enhance reduced food intake(19). However, in GLP-1 receptor–null mice, tirzepatide failed to reduce weight (20), and that implicates a dominant role of the GLP-1 receptor in body weight loss. Still, other studies have shown reduced negative side effects by GIP receptor activation(21). The combination of GIP and GLP-1 receptor agonism in tirzepatide is thought to produce synergistic effects on glucose metabolism and body weight regulation that exceed those of GLP-1 receptor agonists alone(22).

In general, IMDs reduce body weight through two main mechanisms: reducing appetite and calorie intake and slowing gastric emptying(23).

Fat-Free Mass and Lean Body Mass Definitions.

Prior to analyzing FFM and MM loss, terminology should be addressed. In numerous studies, the terms Lean Body Mass (LBM) and FFM are often used interchangeably, which may lead to confusion regarding the parameters being discussed. Recent studies about human physiology show that differentiating between FFM and LBM is senseless. The term LBM was invented to describe the human body more physiologically, but both terms encompass the same components of body composition. This paper will use the term FFM throughout.

Is the FFM and MM loss during weight loss physiological?

For years, science has operated the so-called "Quarter FFM Rule," which states that approximately 25% of weight loss comes from FFM. However, in recent years, this concept has been criticized as too simplified for a complex physiological process. The fraction of weight loss as FFM is not constant but varies based on factors such as initial body composition, diet composition, and the duration of weight loss. Also, influencing factors, such as baseline adiposity, diet composition, metabolic state, aging, inactivity, and exercise, affect FFM loss during weight reduction. Aerobic exercise, combined with dieting, tends to reduce the fraction of weight loss as FFM compared to diet alone. Resistance training can help preserve or even increase FFM during weight loss, especially when combined with adequate protein intake. Periods of physical inactivity can accelerate FFM loss, and older individuals tend to lose more FFM during weight loss due to age-related muscle loss (25). It is not appropriate to consider the loss of FFM and MM during obesity treatment with IMDs as a standard occurrence, given the potential for improved outcomes through a holistic therapeutic approach.

FFM and MM loss in weight loss interventions

Chaston et al.'s systematic review examined this topic in the context of diet, pharmacology, surgery, and behavioral interventions. This was before the widespread use of IMDs, but it will allow us to look at the problem of FFM and MM loss in other therapeutic approaches. Diet and behavioral weight loss interventions led to results in which FFM accounted for 14% to 23.4% of the weight loss, with a higher percentage of FFM loss in males. Bariatric surgery led to a median loss of FFM of 18-31%, depending on the type of operation (26). Other review studies also show that in diet and behavioral body weight

reduction, approximately 20-30% of total weight loss comes from FFM, and MM decreases by about 2-10% with every 8-10% weight loss(27). The studies that searched for mechanisms of FFM and MM loss show that short-term calorie restriction decreases muscle protein synthesis (28,29) However, prolonged moderate calorie restriction increases muscle protein synthesis(30). The loss of MM during prolonged calorie restriction is probably due to increased muscle proteolysis rather than decreased synthesis.

FFM and MM loss in obesity treatment with IMDs.

In the SURMOUNT-1 trial with tirzepatide in the treatment of obesity, the tirzepatide-treated group (5, 10, or 15 mg once weekly) checked by dual x-ray absorptiometry lost 10.9% of their FFM (patients lost 15% to 20.9% of their body weight during the whole trial)(7). It was similar to that reported among the semaglutide-treated participants in the STEP-1 trial(6). As aging-related muscle loss is estimated at 3%-5% per decade after age 30, during these trials, the amount of muscle loss is similar to that of 20 years of aging(31). However, this FFM and MM loss level is similar to that of calory restriction and the bariatric approach to obesity treatment. Some studies show that IMDs positively impact muscle structure and function. For example, tirzepatide treatment in SURPASS-3 significantly improved body weight and fat level without negative effects on the composition of muscles and reduced fat infiltration relative to insulin degludec in people with type 2 diabetes. (32,33) Some studies show that the degree of muscle steatosis (myosteatosis) significantly improved after 6 months of semaglutide therapy. (34) Liraglutide also reduces muscle fat(35). However, there isn't significant evidence that this eliminates the impact of MM loss.

Physical activity in weight loss interventions.

Both resistance and aerobic exercises are recommended as a part of essential obesity care (36) There is enough evidence that the benefits of increased physical activity help maintain a healthy body weight throughout the lifespan and positively impact cardiovascular and respiratory systems and the metabolism of glucose and lipids (37). Some guidelines emphasize the importance of physical activity, especially resistance activity, in preventing MM and strength loss and maintaining proper body weight in months following obesity

therapy(37,38). Exercise may be indicated in older patients with obesity who are at greater risk of sarcopenia. A combination of resistance exercise and a properly selected diet with protein supplementation can give even better results than just exercise(39).

As cited above in Chaston et al.'s systematic review of changes in FFM during significant weight loss, three randomized controlled trials consistently showed that supervised exercises reduced the percentage of weight lost as FFM (%FFML) during low-calorie diets. Aerobic exercise (50-85% of max heart rate for 15-60 min, 5 days/week) reduced %FFML from 27.8% to 13%, resistance training (30 min, 3 days/week) reduced %FFML to 16.6%(26). When selecting activity programs and exercises for patients receiving GLP-1 analogs treatment, we should remember the side effects that may interfere with the patient's ability to participate, like nausea, vomiting, fatigue, and others. Gastrointestinal adverse effects are the most common side effect of GLP-1 analogs and are the most common reason for resigning from treatment(40).

Resistance training is highly effective for preserving MM during weight loss by caloric restriction (41,42). Similar results are found in patients after bariatric surgery(43) Several studies found that progressive resistance exercise training combined with a hypocaloric diet attenuated the loss of MM in middle-aged and older adults with obesity(44–46) Some studies found that vigorous endurance exercise (e.g., 1-hour sessions 6 days/week) helped preserve MM during weight loss(44,47) However, the results are less clear as other studies showed mixed results, with some finding endurance exercise partially preserved muscle compared to diet alone. In contrast, others found no benefits(48).

In a meta-analysis of clinical trials on the effect of diet-induced weight loss on muscle strength in adults with overweight or obesity, seven interventions (108 participants) showed a significant decrease in knee extensor strength measured by isokinetic dynamometry following diet-induced weight loss (49). This highlights the need for strategies to maintain muscle strength during weight loss. As mentioned earlier, IMDs seem to impact muscle structure and function positively, but they need to be researched more deeply.

Physical activity programs should be personalized and consider all patient-specific factors, such as age, accompanying diseases, fitness level, risk factors, and joint mobility.

Incretin-mimetic drugs and exercise to maintain weight loss.

Obesity therapy with IMDs drugs is still new, so there is little information about the long-term effects of these drugs on FFM and MM. However, we already have some information from a randomized controlled trial investigating the effects of exercise, GLP-1 receptor agonist (liraglutide), or their combination on weight loss maintenance in obese adults. We would like to analyze this study because it shows the importance of exercising in body weight maintenance. Before the main study began, participants had undergone an initial 8-week weight loss intervention using a low-calorie diet with an average weight loss of 13.1 kg. Participants who lost at least 5% of their initial body weight were eligible for randomization into the main study. It showed that 52 weeks after the weight loss intervention group, which only exercised, gained 2kg of body mass. Still, compared to placebo, it was -4,1 kg less. Liraglutide proved to be more effective than exercise in maintaining body weight (-0.7kg vs. +2kg) The best way to control the body weight in this trial was a combination of exercises and the liraglutide group with a loss of -3,4 kg. More participants maintained significant weight loss (≥10%) with exercise + liraglutide compared to liraglutide alone.

Changes in FFM and FM were also assessed during this study 52 weeks after weight reduction intervention. The combination group showed a small increase in FFM (+0.5 kg) and the largest decrease in FM (-7.0 kg). In comparison, the group that only exercised had the largest increase in FFM (+1.3 kg) and a significant decrease in FM (-2.5 kg), the liraglutide group experienced a slight decrease in FFM (-1.2 kg) but a substantial decrease in FM (-3.5 kg). The placebo group showed decreased FFM (-1.8 kg) and increased FM (+2.5 kg).

Group	Change in FFM (kg)	Change in FM (kg)
Combination (Exercise +Liraglutide)	+0.5	-7.0
Exercise	+1.3	-2.5
Liraglutide	-1.2	-3.5
Placebo	-1.8	+2.5

Tab. 1. Differences in FFM and FM changes in “Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined” trail groups.

This study designed exercises to reflect the WHO recommendations on physical activity for health: a minimum of 150 minutes per week of moderate-intensity aerobic

physical activity, 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of both. (49) This included 30 minutes of vigorous-intensity, interval-based indoor cycling and 15 minutes of circuit training) two times per week and exercising individually (mainly involves outdoor or indoor cycling, running, or brisk walking) twice weekly(50).

One year after the intervention ended, the post-study follow-up revealed significant differences in weight maintenance and body composition among the four groups. The combination (Exercise + Liraglutide) group regained 7.1 kg during the off-treatment year, had a net weight change from randomization: -3.5 kg, and maintained the most weight loss compared to other groups. The exercise group regained 3.6 kg during the off-treatment year and showed better weight maintenance than liraglutide alone or placebo. The Liraglutide group regained 9.6 kg during the off-treatment year, regained net weight from randomization by 8.7 kg, and experienced the largest weight regain. The placebo group also experienced weight regain, though less than the liraglutide group(51).

The study doesn't provide explicit data on FFM changes for all groups after the one-year follow-up, but after the other results, we can assume that exercising groups maintained more FFM compared to other groups There is a significant role of exercise in maintaining FFM and MM and sustaining weight loss, especially when combined with GLP-1 receptor agonists like liraglutide. (51)

In the STEP-3 trial with semaglutide after 20 weeks, some participants who switched to placebo were compared to others who continued semaglutide treatment experienced a mean body weight change of −7.9% from week 20 to week 68, compared to +6.9% weight gain in those switched to placebo(52).

Both studies show that discontinuing IMDs leads to regaining previously lost weight, but the regain is faster if participants don’t exercise during their treatment. Furthermore, discontinuation of therapy was accompanied by weight regain and the return of cardiometabolic risk factors. Evidence suggests that those effects can be attenuated when therapy is accompanied by supervised exercise.

Nutrition in FFM and MM maintenance.

Guidelines for Obesity Treatment underline the importance of a personalized approach to nutrition. Access to a dietitian or education on appropriate diet are key elements in weight

reduction(37,38,53). During IMDs therapy, patients may have inadequate protein intake due to calorie restriction, so protein consumption should be monitored. Higher protein intake (1.2-1.5 g/kg/day) is recommended during weight loss to help limit MM loss (36,54,55). Guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures recommend a minimal protein intake of 60 g/day up to 1.5g/kg of proper body weight to maintain MM. (56) PROBE study randomized controlled trial examined the effects of a protein-enriched drink on FFM preservation in older adults with obesity and type 2 diabetes. Participants underwent a 3-month lifestyle intervention with dietary advice and resistance exercise. The test group received a drink containing 21g of protein (whey protein enriched with leucine and vitamin D), while the control group received an isocaloric drink without protein. After 3 months, the test group showed an increase in FFM (+0.57 ± 0.27 kg) and appendicular MM (+0.39 ± 0.13 kg). The control group showed no significant FFM or appendicular muscle changes. These results suggest that protein supplementation, particularly when combined with exercise, can help preserve and increase FFM during weight loss interventions in older adults with obesity and T2DM(57). In studies of weight loss diets, 44% of normal protein groups lost ≥30% of their body weight as FFM, compared to only 19-20% in high protein groups(58–60). Protein supplementation beyond the above levels remains unclear, and studies show mixed results(27). No guidelines recommend higher protein doses, but there is still a place for new research on this topic.

Combining diet-induced weight loss with exercise (both endurance and resistance types) helps preserve MM better than diet alone and improves physical function than either diet or exercise alone(44,47).

What does the future hold?

As obesity is one of the biggest public health problems of the 21st century and almost every approach to excessive weight treatments brings the problem of FFM and MM loss, there are also innovative attempts to deal with this problem. Some studies research the topic of selective androgen receptor modulators as the answer for MM loss (61). Recent studies also explore the possibility of targeting alternative signaling pathways for treating obesity. Agents that target myostatin/activin pathways may even increase or maintain MM during the obesity treatment(62,63).

Conclusion.

Obesity therapy with IMDs is becoming more and more common. Besides drugs like liraglutide, semaglutide, or tirzepatide, many other agents in clinical trials promise even better results(64,65). Treatment of obesity with calory reduction and bariatric surgery have shown a positive impact of proper nutrition with high-quality proteins and exercises on maintaining FFM and MM. Studies about obesity treatment with IMDs provided information that exercises help reduce excessive mass and maintain proper body weight. So there are two main principles that help to lose excessive body weight and maintain it in the future that should be in comprehensive therapy of obesity with IMDs. The first is proper nutrition with sufficient protein supply, and the second is physical activity, which combines resistance and endurance exercises. An appropriate specialist should supervise and personalize diet and exercise plans, and if this is not possible, education on these topics should be provided.

Thanks to this approach, holistic therapy for obesity and overweight can be developed, which will help every patient reduce weight and maintain a healthy amount of FFM and MM mass.

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