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Role of physical activity in GLP-1 receptor agonist therapy for obesity treatment

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Abstract

Introduction: WHO recognized it as a global obesity crisis. Globally there are 2,5 billion adult people living with excess body weight (43% of global adult population). Out of these 890 million have obesity disease (16% of global adult population). This forces to implement safe and effective body mass reduction treatment.

Materials and methods: The PubMed database has been searched to perform a literature review that was conducted for scientific purposes focused on high quality studies like randomized trials, meta-analyses, observational cohorts published during the last 5 years (from 2020).

Results: Due to glucagon-like peptide 1 receptor antagonist (GLP-1 RA) pharmacological treatment of obesity became very popular. GLP-1 RAs can induce large initial weight losses. Although a healthy diet and regular physical activity usually lead to 3% to 5% of their body weight reduction they are crucial parts of managing weight. Compilation of GLP-1 RA pharmacotherapy with regular exercises leads to higher effectiveness of body mass reduction with lower reduction of lean body mass. It also makes weight reduction more durable with better metabolic outcomes like enhancing muscle glucose usage and lowering inflammation level. Exercises also contribute to improving general fitness, muscle mass and improvement of cardiovascular condition which improves quality of life of people with obesity disease. The aim of this study is to assess the role of physical activity in a process of weight reduction with use of GLP-1 RA.

Conclusion: Physical activity is complemented with GLP-1 RA as obesity treatment. An intervention of combined pharmacological and lifestyle approach appears to offer the best long-term obesity management.

Keywords: GLP-1 receptor agonists, obesity treatment, liraglutide, semaglutide, tirzepatide, weight loss, physical activity, lifestyle intervention, obesity management

Introduction

Obesity is a chronic, progressive and recurrent chronic disease characterized by an excessive amount of adipose tissue. This clinical condition substantially raises the long-term health risk. It is linked to more than 200 diseases, including development of diabetes, hypertension, cardiovascular disease, cancers, liver and gallbladder diseases, and other comorbidities that reduce a life span [1, 2].

According to the WHO data in 2022 there were 2,5 billion adult people living with excess body weight (43% of global adult population). Out of these 890 million have obesity disease (16% of global adult population) [3]. Due to the consequent rise in obesity prevalence in recent decades, WHO recognized it as a global obesity crisis. In the past 50 years, the problem of obesity has spread as a pandemic. The amount of people suffering from malnutrition is more than doubled by those with obesity disease [4, 5].

Therapy for people with excessive body weight should be structured and multifaceted, including dietary change and physical activity, adapted to the patient's individual situation and capabilities. Patients with obesity disease treatment consists of: dietary treatment, physical activity, behavioral therapy and if needed pharmacotherapy, surgical treatment.
Drugs used in obesity treatment are orlistat, naltrexon with bupropione and a rising in popularity group called glucagon-like peptide-1 receptor agonists (GLP-1 RAs): semaglutide, liraglutide and tirzepatide (which is a dual GIP and GLP-1 receptor agonist). This year (2025) is 20 years since the first GLP-1 RA was registered for diabetes mellitus type 2 (not yet for obesity treatment). In 2010 litaglutide was registered for the same purpose and 4 years later the indications were extended also for obesity treatment [6].
Studies conducted in the United States of America revealed that 12% of the adult population have ever taken GLP-1RA. The number of people with prescriptions for GLP-1 RA rose from 89,267 in 2020 to 597,885 in 2024 [7]. The aim of this study is to assess the role of physical activity in a process of weight reduction with use of GLP-1 RA.

Methods

A literature review that was conducted for scientific purposes focused on high quality studies like randomized trials, meta-analyses, observational cohorts) published during the last 5 years (from 2020). The PubMed database has been searched using following terms: “GLP-1 receptor agonist”, “liraglutide”, “semaglutide”, “tirzepatide”,“physical activity”, “physical exercise”, “weight loss”, and “obesity”. Included free access studies that combined GLP-1 RA treatment with a physical activity intervention. The research excluded pediatric studies.
This review examines evidence from recent trials and analyses on how physical activity interacts with GLP-1 RA therapy in adults with obesity disease, intended on weight loss, metabolic health, exercise capacity, adherence, including long-term success.

Results

GLP-1 RA mechanism

The glucagon-like peptide 1 (GLP-1) is a peptide hormone made from proglucagon. It is mostly produced in the L-cells of the intestine, in certain cells of the pancreas, and acts in the central nervous system on the pro-opiomelanocortin (POMC)/CART neurons that improves satiety, reduce hunger. It also increases insulin release from pancreatic β-cells. GLP-1 lowers glucagon level during high blood sugar. GLP-1 receptor agonists (GLP-1RAs) act like natural GLP-1. They activate GLP-1 receptors, which leads to more insulin release and less glucagon production. When GLP-1 RAs are applied, food passage from stomach to duodenum is slowlier, resulting in faster satiety on one side and less dynamic glucose absorption on the other. GLP-1 RA’s central neuroactivity effects reducing appetite and due to that reducing caloric intake [8, 9, 10]. These actions help keep blood sugar stable, improve blood fat levels, and lower heart disease risk in people with type 2 diabetes and obesity. Due to these effects, GLP-1RAs are useful for lowering blood sugar and managing metabolic syndrome [6].

Therapy with liraglutide also has side effects. The most common is nausea, which may occur with or without vomiting and bloating syndrome. Other less common complications are constipation, diarrhea or feeling of heartburn. Starting the therapy with a low dose and gradually increasing may decrease the risk of gastrointestinal side effects. Compared to placebo liraglutide-based therapy is associated with higher risk of pancreatitis and gallstones [11, 12, 13].

Physical activity

Physical activity is as any bodily movement produced by skeletal muscles that requires energy expenditure [14]. It is crucial for obesity management and is universally recommended with a diet. Regular exercise improves energy expenditure. It also enhances cells' sensitivity for insulin and cardiovascular conditions. Physical exercise therapy's advantage is low-cost and possibility to be adopted as a habit after intervention. Current recommendations advise at least 150-300 minutes of moderate aerobic exercise per week (30-60 minutes daily, minimum 5 times per week) or 75-150 minutes of high-intensity endurance exercise (15-30 minutes daily minimum 5 times per week) [14, 15, 16]. Any physical activity is better than none [17]. Physical activity provides many health benefits beyond just weight loss. These include better heart and lung function, improved mental health, and stronger bones.

The relationship between physical activity and health is a curvilinear pattern. This means that people who start from doing no activity to perform some moderate activity gain the most health benefits. Though in recent years, efforts to encourage people to be more active have grown significantly. These include methods like motivational interviews, smartphone apps, and the use of artificial intelligence. Healthy diet and regular physical activity are crucial parts of managing weight, although they usually lead to 3% to 5% of their body weight reduction [18].

Weight loss efficacy

GLP-1 RAs can induce large initial weight losses. Effectiveness of the therapy depends on many factors like: kind of GLP-1 RA, dose, time of therapy, addiction of physical activity or lifestyle interventions. A body weight loss may achieve 5,7-8,0 % for 3 mg of liraglutide usage [19, 20, 21], 4,9-16 % for semaglutide in a 2,4 mg dose [22, 23] and 15% to 20.9% of body weight reduction for tirzeapatide in dose of 5 mg and 15 mg respectively [24, 25]**.**

A study involving 195 patients with obesity disease who underwent an 8-week low-calorie diet, achieving an average weight loss of 12% then were then randomly assigned to one of four groups: control group (placebo), exercise, liraglutide (3.0 mg/day) or a combination of exercise and liraglutide. The most effective abdominal fat reduction was with a combination of liraglutide and exercise (-6.1 pp), for exercise only (-2.6 pp), and for liraglutide only (-2.8 pp) compared to placebo [26].

Long-Term Success

Weight loss maintenance is crucial for long term health effects. Studies show that almost 50% of patients quit these therapies within a year due to cost or side effects. When pharmacotherapy is discontinued behavioral strategies concerning physical exercise remain. Although GLP-1 RA has impressive effects on body mass reduction after termination of pharmacotherapy weight regain appears and if no behavioural habits were implemented [27, 28].

Participants who completed a one-year long intervention involving regular physical exercise remained more active on their own at one-year follow-up after the intervention [29]. GLP-1 RAs require continuous use to maintain effect, but integrating physical activity may enhance long-term success by both reducing medication dependence and preserving lean body mass [30, 31].

Metabolic Outcomes

In the Jensen et al. study (2023) liraglutide alone improved glucose tolerance modestly, while in combination with exercise improved β-cell function and a reduction in postprandial glucagon response versus placebo [32]. Sandsdal et al. study (2023) reported that physical activity with liraglutide lowered the severity of metabolic syndrome with greater effectiveness than achieved by either alone. The group that underwent combined liraglutide and exercise experienced a 43% reduction in high-sensitivity C-reactive protein versus placebo ($p=0.03$), indicating significantly lower inflammation level. This suggests that combining exercise and GLP-1 RAs results in additive benefits on regulation on glycemia and metabolic risk factors than each one [26].

Physical Function and Exercise Capacity:

For people with obesity disease any weight loss is subjectively perceived as betterment of physical functioning [33]. Exercises contribute to improving general fitness, muscle mass and improvement of cardiovascular condition. It is linked not only to lower risk of death but also to better mobility and possibility to perform everyday tasks. For instance, people with higher fitness levels may find activities like climbing stairs less difficult. These benefits are most often seen in individuals who already have limited mobility, such as older adults with obesity or those with severe (Class II or III) obesity [34]. Exercise performed with supervision resulted in creating a habit for regular physical activity after intervention ended. Due to that weight gain after discontinuation of pharmacotherapy is importantly lower compared to pharmacotherapy without exercises. In Jensen's study, participants who were randomized to supervised exercise maintained higher habitual physical activity and better physical condition one year after the program ended. Two-thirds of their initial weight loss persisted, and they had lower resting heart rate and better functional status than the liraglutide-only group. In contrast, benefits on glucose level and body composition from liraglutide faded after the drug was stopped. These findings imply that exercise training ensures sustainable improvements in physical capacity and general condition that are complemented with the weight-loss effects of GLP-1 RA [9].

Other healt benefits

GLP-1 RA without physical activity support can lead to reduction of body weight but also to loss of muscle mass which may have a detrimental impact on physical functioning, frailty syndrome and sarcopenia due to muscle atrophy. Physical exercises applied with the GLP-1 RA minimizes this effect leading to reducing fat mass, not muscle mass. That effect is especially important particularly among individuals presenting with metabolic dysfunction and obesity [35]. For this population reduced muscle mass constitutes an independent risk factor for both all-cause and cardiovascular disease mortality. GLP-1 RA therapy alone can reduce bone density when applied alone with no physical activity [36].

Low bone mineral density improves risk of fractures. Mortality rates tend to rise after any type of fracture - most notably after hip and vertebral fractures, but also other major fractures. Weight loss–induced bone loss is a significant concern, particularly in older adults. However, research has demonstrated that bone density loss associated with weight reduction occurs not only in the elderly but also during prolonged caloric restriction. Studies show the combination of exercise and GLP-1RA is the most effective weight loss strategy while preserving bone health [37].

Discussion

In a study of 1,961 adults with overweight or obesity and either normoglycemia or prediabetes, semaglutide 2.4 mg combined with lifestyle changes led to a 14.9% average weight loss over 68 weeks. In comparison, the control group receiving placebo with lifestyle changes reduced 2.4% of body weight. The semaglutide-based therapy led to achieving more demanding weight loss targets. 86.4% of participants on semaglutide lost at least 5% of their body weight, compared to 31.5% in the placebo group. The 15% body mass reduction was reached by 50.5% of participants from the intervention group and only 4.9% from the control group [38].

Lundgren et al. found that adults who followed an 8-week diet and were then randomized to 1 year of aerobic exercise plus liraglutide maintained far more weight loss than those on exercise or liraglutide alone. In that trial the group that received a combination of liraglutide treatment and physical activity lost about 9.5 kg, versus 6.8 kg with liraglutide alone and 4.1 kg with exercise alone. Sandsdal et al. similarly reported that adding exercise to liraglutide induced larger decreases in metabolic-syndrome Z-score, abdominal fat and C-reactive protein than either intervention by itself. These findings suggest an additive or synergistic effect: exercise and GLP-1 RA act through complementary pathways to enhance weight loss and improve metabolic parameters [9].

Exercise preserves lean tissue that is often lost with pharmacotherapy. Meta-analysis of GLP-1 RA based treatments like semaglutide and tirzepatide resulted in lean-mass losses which constituted 25% of weight lost [39]. Other sources suggest that the level of lean mass loss may be up to 50% of total weight loss [40, 41].

In contrast, supervised exercise generally increases or preserves muscle mass. Perez-Boj et al. found that combining exercise with anti-obesity drugs yields greater fat loss and better lean-mass retention than drugs alone. In practice, trial participants randomized to exercise-alone gained a small amount of lean mass, and those on combined therapy maintained lean mass despite substantial fat loss. Therefore, adding exercise to GLP-1 RA treatment appears to mitigate the relative loss of lean body mass typical of the pharmacotherapy. This is clinically important, since preserving muscle improves metabolism and function [42].

Combination of GLP-1 RA and physical activity targets both sides of the energy-balance equation. Clinical data support this synergy. Interventions consisted of GLP-1 RA and physical exercises therapy resulted in greater body composition benefits, glycemic improvements, and inflammatory reductions than either intervention alone [26]. In clinical practice, this means patients can achieve superior weight loss maintenance and cardiometabolic improvement by adopting both strategies concurrently.

The durability of weight loss is a particular advantage of the combined approach. Rapid weight regain after drug discontinuation is a major barrier to long-term success with GLP-1 RAs alone [9]. Interventions based on exercises appear more sustainable. Participants retain higher activity levels after the program and have persistent benefits in body composition. Jensen et al. found that nearly two-thirds of the weight lost during the exercise program persisted one year after it ended, whereas those who stopped liraglutide regained most of their weight. If confirmed in larger cohorts, this suggests that embedding an exercise habit during pharmacotherapy could buffer against rebound weight gain when the medication is discontinued.

From a physiological point of view, exercise may counteract some adaptive changes that accompany drug-induced mass reduction. Weight loss typically decreases resting metabolic rate and may lower muscle mass. Exercise can have opposite effects by stimulating muscle preservation and increasing energy expenditure. Moreover, exercise enhances insulin sensitivity and lipid metabolism independently of weight, which could magnify the metabolic gains from GLP-1 RAs. The improvement in β-cell function is seen only with the combined treatment of pharmacotherapy and physical activity [43] is likely to have an effect of lower glucolipotoxicity (from weight loss) and the training effect on pancreatic function. Similarly, reductions in visceral fat with exercise and GLP-1 contribute to lowered inflammation and cardiovascular risk [26].

The available evidence indicates that supervised exercise adds substantially to the benefits of GLP-1 RA therapy in obesity. In randomized trials, combined exercise and GLP-1 RA regimens consistently outperformed either intervention alone.

Gaps and Limitations: Despite these promising results, several limitations and inconsistencies merit mention. Most evidence comes from relatively small trials (largely in Denmark) focusing on liraglutide; comparable large-scale trials of semaglutide or tirzepatide plus exercise have not yet been reported. This suggests that while exercise augments weight maintenance, its independent effect on metabolic syndrome markers may be modest unless combined with GLP-1 therapy. Few trials have reported objective measures of habitual physical activity or cardiorespiratory fitness as outcomes. A recent meta-analysis noted that Randomized control trials of weight-loss drugs did not systematically assess physical activity levels or aerobic capacity. Consequently, it remains unclear how much GLP-1 RA treatment alters actual exercise behavior, or vice versa [41].

Data on other exercise modalities are lacking. No trials to date have specifically tested resistance training, high-intensity interval training, or different exercise intensities in combination with GLP-1 RAs. It remains unclear whether such approaches might further enhance outcomes (e.g. by better preserving muscle mass or improving insulin sensitivity). The extent to which free-living (unsupervised) physical activity or lifestyle-integrated exercise interventions produce similar synergistic effects is also unknown.

Additional uncertainties include the generalizability of findings: the trials largely excluded patients with diabetes or severe comorbidities (except from one HFpEF study), and pediatric populations were excluded by design. Real-world adherence to exercise regimens (outside of clinical supervision) may be lower than in trials. Moreover, as new agents (eg tirzzepatide) enter practice, the interaction with lifestyle interventions may differ. Finally, cost-effectiveness of combined therapy (drug and program) versus drug alone has not been established.

Conclusion

Recent high-quality trials demonstrate that supervised exercise (especially aerobic training meeting recommended 150 min/week) significantly enhances the benefits of GLP-1 RA therapy. GLP-1 RAs reduce energy intake, simultaneously physical activity increases energy expenditure, enhances muscle glucose usage, and improves cardiovascular condition. Exercise plus liraglutide yielded superior weight maintenance, larger fat loss, and greater improvements in glycemic and inflammatory markers than either intervention alone. It is also important that physical exercise grants lasting functional and behavioral gains. Participants who combined exercise with medication after discontinuation of treatment regained less weight and maintained higher activity levels thereafter. This aspect is vital due to the fact that almost 50% of patients quit these therapies within a year due to cost or side effects. Physical activity is complemented with GLP-1 RA as obesity treatment. An intervention of combined pharmacological and lifestyle approach appears to offer the best long-term obesity management. Further research should explore the optimal types and intensities of exercise to pair with GLP-1 RAs (including resistance training and interval work), the generalizability of these findings to more diverse populations, and strategies to improve real-world adherence. In clinical practice, clinicians should reinforce that GLP-1 agonist therapy is most effective when used as part of a comprehensive program that includes regular physical activity, healthy diet, and behavioral support. Future studies and guidelines ought to treat physical activity not just as background advice, but as an integral component that potentiates the success of GLP-1–based obesity pharmacotherapy.

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