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## Current innovative treatments of obesity

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## **ABSTRACT**

Obesity is a complex and pervasive chronic health concern with multifaceted origins in which abnormal or excessive fat accumulation worsens health, increases the risk of long-term medical complications and shortens life expectancy. It is associated with type 2 diabetes, non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease. More than 603.7 million adults are estimated to be obese. The cause of obesity is a long-term energy imbalance caused by a combination of increased energy intake and decreased energy expenditure.

The purpose of this study is to analyze the effectiveness of modern obesity treatments such as intermittent fasting, semaglutide and surgical interventions. Intermittent fasting involves voluntary periods of restricted or zero caloric intake at specified intervals. However, research results on the effectiveness of this dietary strategy are conflicting. The findings indicate that incorporating physical exercise can further enhance the outcomes of applying this diet. Semaglutide, a GLP-1 (glucagon-like peptide-1) analog, has shown efficacy in promoting weight loss among adults and adolescents, along with metabolic and cardiovascular improvements. Laparoscopic sleeve gastrectomy (LSG) is a common bariatric procedure, while Roux-en-Y gastric bypass (LRYGB) is another option. Long-term studies show that both methods effectively promote weight loss.

In conclusion, obesity is a multifaceted condition that requires a comprehensive treatment approach. Individualized strategies including dietary changes, pharmaceutical interventions such as semaglutide, and surgical options can together contribute to effective weight management and improved health outcomes.

**Key words:** obesity; diet; semaglutide; intermittent fasting

## **INTRODUCTION**

Obesity is a complex chronic disease where abnormal or excess fat accumulation impairs health, increases the risk of long-term medical complications, and shortens lifespan [1]. It is defined using the body mass index (BMI) [2]. BMI is adopted as a quick and simple clinical tool to first classify patients into risk categories and to monitor changes in adiposity over time both at the individual and population levels [3]. The Global Burden of Disease Obesity Collaborators estimated that over 603.7 million adults are obese. Furthermore, it was approximated that heightened Body Mass Index (BMI) measurements accounted for 4 million fatalities in the year 2015, with approximately two-thirds of these being linked to cardiovascular ailments [4]. Within the confines of the United States, the occurrence of obesity surged to nearly 40% during the period spanning from 2015 to 2016, as indicated by a comprehensive study conducted on a nationally representative sample, known as the National Health and Nutrition Examination Survey [5].

Several investigations have showcased that obesity isn't a straightforward matter; rather, it's a multifaceted health concern that emerges from the interplay of personal elements (genetics, acquired behaviors) and noteworthy determinants (unhealthful societal or cultural eating patterns, areas devoid of accessible nutritious foods) [17,18]. Some genetic and lifestyle factors influence the likelihood of adult obesity; thus, significant clusters of obesity observed in specific geographic regions and contexts also signal the impact of socio-economic and environmental factors on "obesogenic" environments [19]. Moreover, there is a correlation between obesity and a rising occurrence of various cardiovascular conditions, ranging from elevated blood pressure and coronary heart disease (CHD) to atrial fibrillation (AF) and, in some instances, congestive heart failure [20].

## **OBESITY ETIOLOGY**

The cause of obesity is a long-term energy imbalance caused by a combination of increased energy intake and reduced energy expenditure [12,13,14,15]. The National Health and Nutrition Examination Survey (NHANES) highlighted that the mean daily consumption of energy escalated between 1971 and 2000, registering an uptick of 168 kilocalories (kcal) per day for males and 335 kcal per day for females. In the absence of proactive control or accommodation in energy equilibrium, this augmentation could theoretically elucidate an annual weight gain of eight kilograms in males and 16 kilograms in females. Additionally, energy expenditure has dwindled over the preceding decades [16].

Adipose tissue not only exerts an influence on the central regulation of energy balance, but an excess of adipose tissue can also malfunction and create a predisposition for the emergence of various medical complications, including type 2 diabetes [6], gallbladder disorders [7], non-alcoholic fatty liver disease [8], and gout [9].

The surplus and misplaced fat deposits serve as significant reservoirs for adipokines and inflammatory agents, which have the potential to disrupt glucose and lipid metabolism, consequently elevating the risks of cardiometabolic disorders and certain cancers. This, in turn, can lead to a reduction in disease-free years and life expectancy, ranging from 6 to 14 years [1,10,8]. It has been approximated that around 20% of all cancer cases can be attributed to obesity, regardless of dietary factors [9]. Obesity escalates the likelihood of various cancers, including colon cancer (both genders), kidney cancer (both genders), esophageal cancer (both genders), endometrial cancer (women), and post-menopausal breast cancer (women) [11].

## **MATERIAL AND METHODS**

The aim of this study is to analyze the effectiveness of modern methods for treating obesity. For this purpose, a review of literature from the PubMed database was conducted. Only articles in English were included for further analysis. The keywords used were: "*obesity*", "*diet*", "*semaglutide*", "*surgical obesity treatment*". Ultimately, 10 articles were selected for analysis.

## **MODERN METHODS OF OBESITY TREATMENT**

### *Intermittent fasting*

Fasting is known to be one of the most ancient traditions in the world, and has been practiced among various communities for either cultural or religious reasons. Interestingly, it has also been used as a healing method for diseases in the past. Intermittent fasting pertains to dietary routines that revolve around distinct time intervals, spanning from 12 hours to multiple days, during which minimal or no caloric intake occurs [21,22,23]. This practice is voluntary in nature, adheres to a predetermined timeframe, and typically includes the consumption of calorie-containing beverages at regular intervals. The 16:8 approach represents a variant of time-restricted eating, wherein individuals consume their meals within an 8-hour timeframe and abstain from eating for the remaining 16 hours every day. The 5:2 regimen involves adhering to a regular eating schedule for 5 days each week, without any defined guidelines or

constraints, and then observing 2 days of fasting during which energy intake is limited to approximately 500 kcal.

Conley M. et al. compared the 5:2 diet (2 non-consecutive days with 600 kcal and 5 days of energy intake ad libitum per week) with an energy-reduced diet. After 6 months of intervention, both groups reduced their body weight similarly [5.3 kg (5:2) vs. 5.5 kg (standard)] with no significant difference [24].

The aim of the 2020 randomized controlled trial by Kunduraci et al. was to evaluate the effect of a time-restricted diet on metabolic biomarkers and weight control in adults with metabolic syndrome. The study ultimately included 65 patients aged 18 to 65 years with a body mass index (BMI) of 27.0 kg/m<sup>2</sup> or more. Participants were randomly allocated to an intermittent energy restriction (IER) intervention group (n=32) or a continuous energy restriction (CER) control group (n=33). The study lasted 12 weeks. The results of the trial suggest that changes in weight and body composition were similar in both groups. There were statistically significant reductions in blood pressure, total cholesterol, triglycerides, low-density lipoprotein (LDL), fasting glucose and insulin in both groups (p<0.01). However, no significant differences in metabolic syndrome biomarkers were observed between the IER and CER groups. This leads to the conclusion that the intermittent energy restriction diet was not significantly better than the continuous energy restriction diet [25].

A comprehensive examination involving a systematic review and meta-analysis of randomized controlled trials (RCTs) delved into the comparison between intermittent and continuous energy restriction concerning weight loss and cardio-metabolic outcomes. This analysis encompassed eleven trials spanning durations of 8 to 24 weeks and demonstrated a comparable level of weight loss in both intervention groups [26]. Intermittent fasting yielded weight loss results analogous to continuous energy restriction and parallel improvements in cardio-metabolic parameters [27,28,29]. Notably, a recent Cochrane review conducted by Allaf et al. unveiled that individuals achieved greater weight loss through intermittent fasting approaches as compared to not adhering to a specialized dietary regimen over a three-month period. This conclusion was drawn from evidence from seven studies encompassing 224 participants. However, when intermittent fasting strategies were juxtaposed with energy-restricted diets for three months (as evidenced by 10 studies involving 719 participants) or extended durations of 3 to 12 months (as depicted in 4 studies comprising 279 participants), the disparity in weight loss became indistinct [30]. The energy restriction causes the positive effect of intermittent fasting on weight loss, not fasting as a stand-alone intervention [31,32].

A limited-scale study involving eleven overweight participants explored the effects of early time-restricted fasting, where eating occurred within the time span of 8 a.m. to 2 p.m. The investigation focused on acute impacts on glucose metabolism and gene expression. In comparison to the control group, which followed an eating schedule from 8 a.m. to 8 p.m., the group practicing early time-restricted fasting exhibited reduced 24-hour glucose levels and diminished glycemic fluctuations. In the morning before breakfast, there were elevated levels of ketones, cholesterol, and the expression of certain genes related to stress response and aging, notably sirtuin 1 (SIRT1) and microtubule-associated protein 1 light chain 3 alpha (LC3A). It's important to note that this gene expression pattern diverged from the observed pattern in the evening.

Kotarsky et al. reached a different conclusion in a 2021 randomized controlled trial. The authors examined the effects of time-restricted eating (TRE) and concurrent physical training on body composition, cardiometabolic biomarkers, hormones and muscle performance. The study included a total of 21 patients aged 35 to 60 years with a body mass index (BMI) between 25.0 and 34.9 kg/m<sup>2</sup>. They were randomly assigned to either the TRE diet strategy group (n=11) or the normal nutrition (NE) group (n=10). The TRE participants consumed all calories between 12:00 p.m. and 8:00 p.m. The others maintained their previous eating habits. The study lasted 8 weeks. Results suggest that total weight loss was significantly greater for TRE (3.3%) compared to NE (0.2%) before and after the intervention. Moreover, there was a significantly greater loss of fat mass in the TRE group (9.0%) compared to NE (3.3%). This leads to the conclusion that the use of TRE and concomitant physical training may be an effective strategy for reducing body weight in overweight and obese adults [37].

### *Wegovy (semaglutide)*

Semaglutide is a glucagon-like peptide 1 (GLP-1) analogue that is registered, in doses up to 1 mg administered subcutaneously once a week, for the treatment of type 2 diabetes in adults and for reducing the risk of cardiovascular incidents in people with type 2 diabetes and cardiovascular disease. Wilding JPH et.al in their study, investigated the effectiveness of once-weekly semaglutide use in overweight and obese individuals. In this double-blind trial, 1961 adult participants with a body mass index (BMI) equal to or greater than 30 kg/m<sup>2</sup> ( $\geq 27$  kg/m<sup>2</sup> for individuals with at least one weight-related coexisting condition) and without diabetes were enrolled. They were randomly assigned in a 2:1 ratio to receive either a once-weekly subcutaneous dose of semaglutide (at a dose of 2.4 mg) or placebo, alongside a lifestyle intervention, for a duration of 68 weeks. The main goals of the study were to

examine the percentage change in body weight and weight reduction of at least 5%. A remarkable 94.3% of participants completed the study. The trial demonstrated that semaglutide has a positive impact on weight loss. Individuals receiving semaglutide achieved significantly greater weight loss compared to the placebo group. This effect was evident from the beginning of the study and persisted up to the 68th week. Participants receiving semaglutide had a significantly higher likelihood of achieving various percentage-based reductions in body weight, further underscoring the treatment's effectiveness. Semaglutide positively influenced several health parameters, including waist circumference, body mass index (BMI), and blood pressure. It also led to improvements in metabolic indicators, such as fasting serum glucose levels, glycated hemoglobin, C-reactive protein, and fasting lipid levels. This highlights the medication's potential for enhancing diabetes control and overall metabolic health [33].

In another study, a once-weekly subcutaneous dose of 2.4 mg of semaglutide was administered [34]. The aim of this study was to examine the effects of semaglutide in a group of obese adolescents. The study involved 201 participants, and 180 completed the study, which corresponds to 90%. In the 68th week, a total of 95 out of 131 participants (73%) in the semaglutide group achieved a weight loss of 5% or more, compared to 11 out of 62 participants (18%) in the placebo group. Similarly, in this study, at the end of the 68th week, levels of glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, and ALT were lower in the semaglutide-taking group than in the placebo-receiving group [34]. Taking into account the results of these two studies, it can be concluded that semaglutide is an effective medication both in the adult and adolescent populations.

As semaglutide is a new drug, it is important to determine its effect on cardiovascular risk in patients with type 2 diabetes. This issue was addressed by Merso SP et al. in their 2016 double-blind, placebo-controlled randomized controlled trial. The study included 3297 patients aged 50 years or older with type 2 diabetes on a standard treatment regimen. Participants were randomly allocated to a group receiving once-weekly semaglutide 0.5 mg or 1 mg or to a placebo group. The study lasted 104 weeks. The results of the trial suggest that patients treated with semaglutide had a 26% lower risk of a cardiovascular event - cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (HR 0.74; 95% CI 0.58-0.95;  $p < 0.01$ ). The lower risk was mainly due to a significant reduction in the incidence of non-fatal stroke (HR 0.61; 95% CI 0.39-0.99;  $p = 0.04$ ) and a non-significant reduction in

the incidence of myocardial infarction (HR 0.74; 95% CI 0.51-1.08; p=0.12). The proportion of deaths from cardiovascular causes was similar in both groups. This confirms the superiority of semaglutide over placebo [35].

The aim of the 2022 randomized, open-label, phase 3b trial by Rubino DM et al. was to compare the efficacy of semaglutide administered subcutaneously once weekly at a dose of 2.4 mg with liraglutide administered subcutaneously once daily at a dose of 3.0 mg in overweight and obese patients (both in combination with diet and physical activity). The study included 338 patients above the age of 18 with a body mass index (BMI) of 30 kg/m<sup>2</sup> or more or 27 kg/m<sup>2</sup> or more with at least one weight-related comorbidity (e.g., hypertension). Participants were assigned to a group receiving semaglutide (n=126) or liraglutide (n=127) or placebo (n=85). The study lasted 68 weeks. Results suggest that the mean change in body weight from baseline was -15.8% for semaglutide vs. -6.4% for liraglutide (difference -9.4 percentage points; 95% CI -12.0 to -6.8; p<0.001). For placebo, the weight change was -1.9%. This raises the conclusion that among overweight or obese adults semaglutide administered once a week subcutaneously compared to liraglutide administered once a day, combined with diet and physical activity, leads to greater weight loss [39].

### *Surgical treatment of obesity*

Laparoscopic sleeve gastrectomy (LSG) is the most common procedure in the field of bariatric and metabolic surgery, accounting for up to 60% of all bariatric procedures globally. The shift towards the prominence of LSG occurred before long-term outcomes from randomized clinical trials (RCTs) comparing the results, safety, and technical feasibility of LSG with the traditional Roux-en-Y gastric bypass (LRYGB) procedure were available. Bariatric surgery remains the only effective means to achieve sustained and substantial weight loss, resolution of obesity-related comorbidities, improved quality of life, and increased life expectancy. In their study, Salminen P et.al compared the effects of laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB) on weight loss and comorbidities after a 10-year period in adult patients with obesity. In 10-year observation, patients were evaluated in a multicenter, randomized clinical trial called Sleeve vs Bypass (SLEEVEPASS). The study included 240 patients aged 18 to 60 years, with a median body mass index (BMI) of 44.6 kg/m<sup>2</sup>. Participants were randomly assigned to the LSG group (n=121) and the LRYGB group (n=119). A total of 193 patients completed the weight loss observation (85%). The average excess weight loss (%EWL) was 43.5% after LSG and 50.7% after LRYGB, with a difference of 8.4 percentage points between them in favor of LRYGB (95% CI 3.1-13.6).



This demonstrates the effectiveness of both methods described in this study. LRYGB resulted in greater weight loss, but the difference was not clinically relevant [36].

There is now emerging work investigating early metabolomic changes in response to GLP-1RA (glucagon-like peptide 1 receptor agonist) vs. placebo therapy compared to bariatric surgery. To this end, Angeldi et al. 2023 conducted three clinical trials: a cohort study of bariatric surgery [Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG)] and two double-blind, placebo-controlled randomized controlled trials comparing liraglutide to placebo. This was the first study to provide a direct comparison of the early metabolomic, lipid and lipoprotein effects of surgical and pharmacological methods of weight control. The results of the trial suggest that significantly more pronounced effects on metabolites and lipoprotein parameters were observed in the bariatric surgery group with significant changes in lipoprotein lipids, glucose homeostasis, inflammatory markers and ketone bodies. However, after adjustment for body weight, most of the changes were eliminated, making the results between bariatric surgery and liraglutide very similar. The only significant differences were in acetoacetate,  $\beta$ -hydroxybutyrate and citrate [38].

## CONCLUSIONS

In conclusion, the practice of intermittent fasting has gained significant attention as a dietary strategy with potential benefits for weight management and metabolic health. Various approaches, such as the 16:8 and 5:2 regimens, have been explored, often yielding comparable weight loss results to traditional energy-restricted diets. However, it's important to note that the positive impact of intermittent fasting on weight loss seems to stem from fasting alone. Research indicates that in addition to diet, incorporating exercise can lead to better results when implementing this dietary approach.

Semaglutide, a glucagon-like peptide 1 (GLP-1) analogue, has shown promise as a novel therapeutic option for weight management in both adults and adolescents. Studies have demonstrated its effectiveness in promoting substantial weight loss, along with improvements in metabolic parameters and cardiovascular risk factors. These findings underscore the potential of semaglutide to address the challenges of obesity and related health complications.

In the realm of surgical treatment for obesity, laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB) have emerged as prominent procedures. Long-term studies comparing these techniques have indicated sustained weight loss benefits for both

methods. These surgical interventions also offer significant improvements in comorbidities and quality of life.

When examining the effects of GLP-1 receptor agonist therapy and bariatric surgery, studies have shown that bariatric surgery leads to more pronounced metabolomic and lipoprotein changes, though many of these differences are attenuated after accounting for weight loss. Bariatric surgery's impact on various metabolic markers underscores its potential as a powerful intervention for both weight management and metabolic health.

In summary, the diverse approaches discussed in this review article, including intermittent fasting, semaglutide therapy, and bariatric surgery, offer valuable strategies to address the complex challenges posed by obesity and its associated health risks. These interventions provide a multifaceted toolkit for healthcare practitioners and individuals seeking effective ways to manage weight, improve metabolic health, and enhance overall well-being.

### **Author Contributions**

Conceptualization, D.W. and A.G.; Methodology, D.W.; Validation, D.W., A.G. and J.W.; Formal Analysis, D.W., Z.R.; Investigation, D.W. and A.G.; Resources, D.W. and J.W.; Data Curation, A.G., Z.R. and J.W.; Writing – Original Draft Preparation, D.W. and A.G.; Writing - Review & Editing, D.W., A.G., J.W. and Z.R.; Visualization, D.W.; Supervision, D.W., A.G. and J.W.; Project Administration, D.W. All authors have read and agreed with the published version of the manuscript.

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## Conflicts of Interest

The authors declare no conflict of interest.

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