

Comparative Efficacy of Lifestyle Modifications versus Pharmacotherapy on Weight Loss and Metabolic Health Outcomes: A Comprehensive Review

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Abstract

Background: Obesity has become a serious global public health challenge, given that it leads to various adverse health outcomes that include cardiovascular illnesses, diabetes, and certain types of cancer. The World Health Organization (WHO) has estimated that, at the end of 2022, 1 out of every 8 individuals were obese, and that the global adult obesity rates have over doubled since 1990, even as the adolescent obesity rates have quadrupled. Thus, as of 2022, nearly 2.5 billion adults, aged 18 years and above, were overweight, with 890 million being obese. Obesity and overweight incidence rate has been gradually increasing over the years, presenting significant challenges to the healthcare systems throughout the globe. In this regard, the objective of this systematic review was to evaluate the effectiveness and safety of lifestyle modifications (diet and physical activity) and pharmacotherapy in promoting weight loss and improving metabolic health in overweight adults. **Methodology:** To attain the above stated study objective, a systematic evaluation of previous studies was carried out, particularly studies that assessed the

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effectiveness and safety of lifestyle modifications (diet and physical activity) and pharmacotherapy in promoting weight loss and improving metabolic health in overweight adults. The authors have used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in the selection of eligible studies for inclusion in the study. **Results:** The findings indicate that lifestyle interventions resulted in 5% - 10% weight reduction and significant improvements in metabolic indicators, while pharmacotherapy (GLP-1 receptor agonists) achieved up to 15% weight reduction and considerable metabolic health benefits. Further, comparative studies show lifestyle modifications provide overall health benefits, while medication is necessary for non-responders. **Conclusion:** Individualized treatment strategies are crucial, and further research is needed on long-term consequences and combination therapies.

Keywords

Obesity, Overweight, Weight Loss, Pharmacotherapy, Glucose Metabolism Disorders

1. Introduction

Obesity is a serious worldwide public health issue that leads to a range of negative health consequences, including cardiovascular illnesses, diabetes, and certain types of cancer. It is characterized by an abundance of fatty tissue, which interferes with metabolic and hormonal processes, resulting in a series of health problems [1] [2]. The incidence of obesity has been progressively rising, presenting significant difficulties for healthcare systems globally [1] [2]. Obesity's influence on reproductive health is severe, disrupting hormonal balance and ovulatory function, leading to infertility concerns, particularly among women of reproductive age [1] [2]. Addressing obesity is crucial not just for overall health but also for enhancing reproductive outcomes.

1.1. Importance of Weight Loss in Managing Obesity-Related Comorbidities

Reducing weight is an essential component in the treatment of obesity-related comorbidities. Effective weight reduction lowers the chance of developing type 2 diabetes, hypertension, and other metabolic problems [1]-[3]. Furthermore, in reproductive-aged women, weight loss has been demonstrated to increase ovulation rates and hormonal profiles, boosting fertility results [1]-[3]. The decrease in adipose tissue helps to reduce the negative feedback processes on the hypothalamic-pituitary-ovarian axis, which is critical for restoring normal reproductive function [1]-[3]. Therefore, attaining and sustaining weight reduction is vital for minimizing the health risks associated with obesity and increasing the quality of life.

1.2. Overview of Lifestyle Modifications and Pharmacotherapy as Weight Loss Strategies

Changes in lifestyle and pharmacotherapy are two key techniques adopted for weight reduction in patients with obesity. Lifestyle therapies, including dietary adjustments and increased physical activity, are crucial and may lead to lasting weight reduction when followed diligently [1]-[3]. Dietary adjustments commonly entail lowering caloric intake and enhancing the nutritional quality of the diet, while exercise assists in burning calories and boosting metabolic health [1]-[3]. Pharmacotherapy, comprising the use of weight-lowering medicines and ovulation inducers, may be especially effective for people who fail to reduce weight via lifestyle modifications alone [1]-[3]. Combining these treatments may produce synergistic effects, maximizing weight reduction and boosting metabolic and reproductive health outcomes.

2. Materials and Methods

A thorough search of databases, including Oxford Academic, PubMed, Elsevier, Journal of American Heart Association (JAHA), Frontiers, and Science Direct, was done to find relevant articles published in the last 10 years. The inclusion criteria centered on randomized controlled trials, cohort studies, and meta-analyses that examined lifestyle changes with medication in overweight and obese patients. 21 studies were chosen based on relevance, quality, and the robustness of their intervention, as shown in **Figure 1** below. Data extraction included compiling information on weight reduction results, metabolic health markers, safety profiles, and patient adherence from the recognized research.

3. Results

3.1. Lifestyle Modifications

Among the notable aspects of lifestyle modifications is dietary changes. Thus, various types of diets have been examined with regard to their impacts on weight control and metabolic health. For instance, low-carbohydrate diets, including Atkins and ketogenic diets, have been acknowledged to promote a reduction in carbohydrate intake and an increment in fat consumption, prompting the body to burn fat for energy [4]. Further, the Mediterranean diet, which includes fruits, vegetables, whole grains, and healthy fats, has been acknowledged to foster cardiovascular health while aiding weight reduction [4]. Intermittent fasting has also been found to be effective in reducing the total calorie consumption and increasing insulin sensitivity [4]. Low-fat diets, previously the gold standard for weight control, limit fat intake while stressing increased consumption of carbohydrate [4]. The above diets provide distinctive approaches to macronutrient balance and calorie intake, catering to varied tastes and metabolic reactions. For instance, while certain individuals may prefer intermittent fasting as it is simple to follow owing to its regulated eating periods, others might prefer the Mediterranean diet owing to its flexibility.

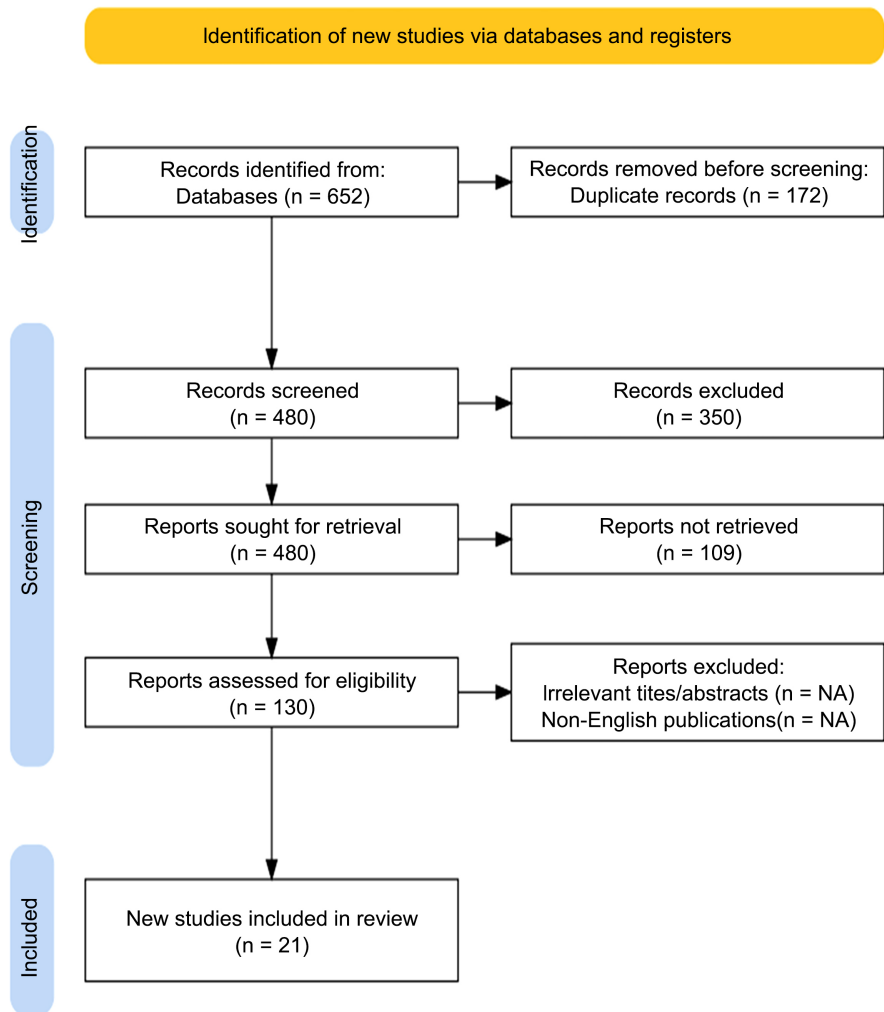


Figure 1. PRISMA flow diagram indicating the study/literature selection process for this systematic review.

Regarding the mechanisms of action for dietary changes, it is noteworthy that dietary adjustments aid weight reduction through processes that include caloric deficit and nutrient composition. Thus, a caloric deficit, where energy intake is less than energy expenditure, is key to all successful diets [4]. This shortfall causes the body to consume stored fat for energy, resulting in weight loss. Nutrient composition also plays a key role; high-protein diets may promote satiety and thermogenesis, making it simpler to sustain a calorie deficit. Low-carbohydrate diets lower insulin levels, which may promote fat burning [4] [5]. Conversely, diets high in fiber, like the Mediterranean diet, decrease stomach emptiness and prolong sensations of fullness. Intermittent fasting may promote metabolic flexibility, enabling the body to swing between burning glucose and fat more effectively [4] [5]. These diets target metabolic pathways to maximize weight reduction and enhance overall metabolic health by changing macronutrient ratios and eating habits.

Moreover, regarding the impacts on weight loss and metabolic health, it can

be noted that different dietary methods have varying benefits on weight reduction and metabolic health. Low-carbohydrate diets frequently result in quick initial weight reduction owing to lower glycogen storage and accompanying water loss, and they may enhance insulin sensitivity and lipid profiles [5]-[8]. The Mediterranean diet, although low in weight reduction pace, considerably increases cardiovascular health, decreasing the risk of heart disease and stroke owing to its high quantity of anti-inflammatory foods [5]-[8]. Intermittent fasting has been found to enhance glucose metabolism, possibly lowering the incidence of type 2 diabetes. Low-fat diets, however less successful in the short term compared to low-carb diets, may nonetheless yield considerable weight reduction and improve lipid profiles over time [5]-[8]. Each diet's efficacy in increasing metabolic health is also impacted by individual adherence, hereditary variables, and pre-existing health issues, underscoring the need for tailored dietary advice.

The other notable aspect of lifestyle modification assessed in this study is physical activity. Thus, physical activity is an essential component of weight control and metabolic health, covering aerobic workouts, strength training, and high-intensity interval training (HIIT). Aerobic workouts, such as walking, jogging, and cycling, boost cardiovascular fitness and burn calories [6]-[10]. Resistance exercises, such as weightlifting and bodyweight workouts, focus on growing muscle mass, which boosts the resting metabolic rate and promotes fat loss [6]-[10]. HIIT alternates between brief bursts of intense activity and intervals of rest or low-intensity exercise, optimizing calorie burn in a shorter time and boosting both aerobic and anaerobic performance [6]-[10]. All kinds of physical exercise have distinct advantages and may be customized to individual fitness levels and tastes, giving a complete approach to physical fitness and weight control.

Concerning the mechanisms of action, it is noteworthy that the approaches through which physical exercise benefits weight reduction and metabolic health are diverse. For instance, aerobic exercise boosts energy expenditure during activity and for a brief time, thereafter, providing a caloric deficit important for weight reduction [8]-[13]. It also promotes cardiovascular health by boosting heart and lung efficiency. Resistance exercise helps keep and grow muscle mass, which is vital for maintaining a higher resting metabolic rate, therefore supporting long-term weight control [8]-[13]. Muscle tissue burns more calories at rest compared to fat tissue, making muscle maintenance crucial for weight reduction [8]-[13]. HIIT combines the advantages of both aerobic and anaerobic training, boosting energy expenditure and enhancing metabolic flexibility [8]-[13]. The after-burn effect, or excess post-exercise oxygen consumption (EPOC), is more significant with HIIT, leading to increased calorie burn long after the session is over.

Consequently, regarding the impact of physical activity on weight loss and metabolic health, it can be noted that physical exercise greatly improves weight reduction and metabolic health. Regular aerobic exercise improves glucose me-

tabolism, decreases the risk of type 2 diabetes, and boosts cardiovascular fitness, lowering the risk of heart disease [8]-[13]. Resistance exercise, by increasing muscle mass, improves sustained weight reduction and metabolic health by enhancing resting metabolic rate and improving body composition [8]-[13]. HIIT is especially effective in lowering visceral fat, a critical risk factor for metabolic diseases, and in increasing insulin sensitivity [8]-[13]. Physical exercise also favorably improves mental health by lowering feelings of anxiety and depression, which may indirectly benefit weight control efforts [8]-[13]. Overall, combining multiple forms of physical exercise into a lifestyle change strategy offers overall health benefits and increases the possibility for long-term weight control and enhanced metabolic health.

Lastly, pharmacotherapy as weight loss approach or strategy entails the use of various kinds of medication to reduce weight in obese and overweight persons. Thus, the most frequently employed weight reduction drugs include orlistat and GLP-1 receptor agonists such as liraglutide and semaglutide. Orlistat (Xenical, Alli) works by limiting the absorption of dietary fats in the gut, resulting in decreased calorie intake [14] [15]. GLP-1 receptor agonists, including liraglutide (Saxenda) and semaglutide (Wegovy), imitate the incretin hormone GLP-1, which stimulates insulin production, slows stomach emptying, and induces satiety [14] [15]. Other drugs, such as phentermine-topiramate (Qsymia) and naltrexone-bupropion (Contrave), can help with weight reduction by reducing appetite and boosting energy expenditure.

Regarding pharmacotherapy's mechanisms of action, it can be noted that Orlistat's major mode of action is the suppression of pancreatic lipase, an enzyme important for the breakdown of triglycerides in the gut. This leads to around 30% of dietary fat being excreted undigested [14] [15]. GLP-1 receptor agonists act by imitating the incretin hormone, which increases insulin production, slows stomach emptying, and suppresses hunger, resulting in decreased food consumption [14] [15]. Phentermine-topiramate operates on the central nervous system to reduce appetite, whereas naltrexone-bupropion alters the brain's reward circuits linked with food cravings.

Further, regarding the impact on weight loss and metabolic health, pharmacotherapy has been scientifically proven effective in weight reduction and enhancement of metabolic health indices. Orlistat use has been acknowledged to bring about a 5% - 10% reduction in body weight over a period of 1 year [14] [15]. However, GLP-1 receptor agonists, including liraglutide and semaglutide, have been reported to result in even higher weight reduction, with some patients losing 10% - 15% of their body weight [14] [15]. These drugs also enhance metabolic parameters, such as decreasing HbA1c levels in individuals with type 2 diabetes, lowering blood pressure, and boosting lipid profiles [14] [15]. Phentermine-topiramate and naltrexone-bupropion also indicate positive changes in metabolic health, while their principal advantages are weight reduction and suppression of appetite.

3.2. Comparative Analysis

In comparing the short-term and long-term efficacy of lifestyle modifications in relation to pharmacotherapy in weight loss, our study findings have disclosed that lifestyle improvements, such as changes in diet and higher physical activity, generally lead to an average weight reduction of 5% - 10% of starting body weight between six months and years [1]-[21]. Pharmacotherapy may accelerate weight reduction beyond lifestyle modifications alone, with drugs like GLP-1 receptor agonists promoting 10% - 15% weight loss over the same time [1]-[21]. Nevertheless, maintaining the weight reduction results remains problematic for both techniques, with a substantial chance of weight rebound unless continuing intervention and support are offered.

Still, regarding the comparative impact on metabolic health outcomes, the study has disclosed that combining lifestyle adjustments and therapies improves metabolic health. Lifestyle treatments increase insulin sensitivity, and lipid profiles, and lower cardiovascular risk factors [1]-[21]. Pharmacotherapy, especially with GLP-1 receptor agonists, considerably decreases HbA1c levels and reduces the risk of cardiovascular events [1]-[21]. The combined approach of lifestyle adjustments with medicine frequently leads to better improvements in metabolic health compared to either method alone.

Table 1. Outcome comparison of the studies included in this systematic review.

Study	Intervention	Weight Loss (%)	Metabolic Health Outcomes	Adverse Effects	Adherence	Notes
1) Ruiz-González <i>et al.</i> , 2024	Exercise, diet, pharmacotherapy	Exercise: 5% - 8%	Improved HbA1c, BP, lipid profiles	Minimal for exercise/diet, moderate for drugs	High for lifestyle	Individualized approaches recommended
2) Lee <i>et al.</i> , 2019	Pharmacotherapy, lifestyle	Pharmacotherapy: 10% - 15%	Decreased HbA1c, BP	GI issues, nausea	Moderate for drugs	Cost-effectiveness analysis included
3) Wadden <i>et al.</i> , 2020	Lifestyle modification	5% - 10%	Improved insulin sensitivity, cardiovascular risk	Low	Variable	Focus on psychological support
4) Otto <i>et al.</i> , 2018	Dietary diversity	5% - 7%	Improved lipid profiles	Minimal	High	Focus on prevention
5) Isaacs <i>et al.</i> , 2016	GLP-1 receptor agonists	10% - 15%	Improved HbA1c, BP, weight loss maintenance	GI side effects	Moderate	Role in obesity management
6) Birk <i>et al.</i> , 2024	Exercise, GLP-1 RA	10% - 15%	Maintained weight loss, improved insulin sensitivity	GI side effects	Moderate	Combination treatment effectiveness
7) Vosoughi <i>et al.</i> , 2022	GLP-1 agonists	12% - 15%	Improved HbA1c, lipid profiles	Moderate GI issues	Moderate	Meta-analysis results

Continued

8) Vosoughi <i>et al.</i> , 2021	GLP-1 analogs	11% - 14%	Improved metabolic markers	Moderate GI issues	Moderate	Focus on safety and efficacy
9) Zaccardi <i>et al.</i> , 2015	GLP-1 RA	10% - 15%	Improved metabolic health	GI issues, pancreatitis (rare)	Moderate	Benefits vs. harms analysis
10) Singh <i>et al.</i> , 2019	Anti-obesity drugs	10% - 12%	Improved metabolic outcomes	Varied per drug	Moderate	Systematic review findings
11) Liu <i>et al.</i> , 2023	GLP-1RAs	10% - 15%	Improved HbA1c, lipid profiles	GI side effects	Moderate	Systematic review and meta-analysis
12) Popoviciu <i>et al.</i> , 2023	GLP-1 agonists	10% - 15%	Improved HbA1c, reduced weight	GI side effects	Moderate	RCT review
13) Rao <i>et al.</i> , 2019	Exercise, pharmacotherapy	Exercise: 5% - 7%	Improved insulin sensitivity, visceral fat reduction	Minimal	High for lifestyle	Meta-analysis on visceral adiposity
14) Taha <i>et al.</i> , 2022	GLP-1 RA	12-15%	Improved metabolic markers	GI issues	Moderate	Comprehensive review
15) Zhu <i>et al.</i> , 2021	GLP-1 RA	10-13%	Improved HbA1c, NAFLD improvement	GI side effects	Moderate	Focus on NAFLD
16) Bouzas <i>et al.</i> , 2023	GLP-1 RA, DPP-4 inhibitors, metformin	10% - 15%	Improved metabolic syndrome parameters	Minimal to moderate	Moderate	Comparative analysis
17) Elmaleh-Sachs <i>et al.</i> , 2023	Obesity management strategies	5% - 15%	Varied	Varied	Varied	Comprehensive review
18) Kushner, 2018	Lifestyle, pharmacotherapy	5% - 10% for lifestyle, 10% - 15% for pharmacotherapy	Improved metabolic health	Varied	Varied	Review on strategies
19) Maki <i>et al.</i> , 2023	Pharmacotherapy	10% - 15%	Improved cardiovascular risk	Varied per drug	Moderate	Cardiovascular focus
20) Bessesen <i>et al.</i> , 2018	Anti-obesity pharmacotherapy	10% - 15%	Improved metabolic health	Varied per drug	Moderate	Progress and challenges
21) Song <i>et al.</i> , 2024	Anti-obesity medications	10% - 15%	Improved metabolic health	Varied per drug	Moderate	Real-world practice

Further, concerning the safety profiles and side effects of pharmacotherapy, the study has disclosed that lifestyle adjustments typically have a good safety profile with few adverse effects, while excessive physical activity may lead to injury if not carefully controlled. Pharmacotherapy, although beneficial, comes with possible negative effects [1]-[21]. Orlistat may induce gastrointestinal disorders such as steatorrhea [1]-[21]. GLP-1 receptor agonists may produce nausea, vomiting, and, in rare circumstances, pancreatitis [1]-[21]. Phentermine-topiramate may increase heart rate, sleeplessness, and paresthesia, whereas naltrexone-bupropion may produce raised blood pressure and mental symptoms.

Lastly, on patient adherence and quality of life considerations, compliance with lifestyle improvements might be hard due to the major behavioral changes needed. Constant inspiration and support are vital for long-term success [1]-[21]. Pharmacotherapy may increase adherence to weight reduction regimes by giving extra help in lowering hunger and food consumption [1]-[21]. Nevertheless, side effects and the expense of drugs may hinder long-term adherence [1]-[21]. Quality of life typically improves with weight reduction via both treatments, but tailored strategies including patient preferences, lifestyle, and possible hurdles are needed for sustained success. This has been aptly captured in **Table 1**.

4. Discussion

Our study findings indicate that lifestyle adjustments and medicines are capable of bringing about weight reductions and increases in metabolic health. Lifestyle therapies, including dietary modifications and increased physical activity, have been found to generate an average weight reduction of 5% - 10% of baseline body weight over a period of 6 months to 1 year [17]-[20]. Consequently, pharmacotherapy, especially GLP-1 receptor agonists like semaglutide, have additionally been found to bring about comparable or even higher weight loss, with the findings of different studies indicating reductions of up to 15% of the original weight [17]-[20]. The two techniques, lifestyle therapies and pharmacotherapy, also enhance metabolic markers, including HbA1c levels and blood pressure, but in distinct ways.

4.1. Strengths and Limitations of This Study

Among the key strengths of this study include the observation that it has substantial evidence based on several randomized controlled trials and meta-analyses, offering high-quality data on the effectiveness and safety of lifestyle modifications and medication in relation to weight loss. Further, the study has also utilized long-term research, including the Diabetes Prevention Program and Look AHEAD, which has not only provided vital information but also enhanced the generalizability of the findings [17]-[20]. Regardless of the above strengths, a number of limitations have been acknowledged, including the unpredictability

of patient adherence, the risk of weight gain, and the adverse drug effects [17]-[20]. Therefore, additional studies are required to understand the long-term durability of these therapies and to create techniques to increase adherence and decrease the adverse effects of treatments.

4.2. Practical Implications for Clinicians and Patients

Based on the findings, there is a need for clinicians to adopt a tailored strategy when advising weight reduction treatments, and combining lifestyle adjustments with pharmacotherapies where needed. Regular follow-up and assistance are also necessary to sustain weight reduction and enhance metabolic health [17]-[20]. Educating patients on the advantages and possible adverse effects of drugs, in addition to giving them behavioral support alternatives, is more likely to boost adherence and results [17]-[20]. Patients should be encouraged to set realistic goals and participate in persistent lifestyle modifications to accomplish and sustain their weight reduction.

4.3. Recommendations

It is recommended that clinicians should emphasize lifestyle adjustments as the first-line therapy for obesity owing to their broad health benefits and few adverse effects. Pharmacotherapy should be explored for individuals who do not achieve substantial weight reduction with lifestyle modifications only, and also for those with obesity-related comorbidities needing more rapid interventions [18]-[20]. Furthermore, it is vital that treatment approaches are customized based on individual patient's traits, preferences, and medical history [18]-[20]. Continuous monitoring and assistance are needed to guarantee adherence and treat any possible adverse effects of medication, enhance patient outcomes and support long-term weight control [18]-[20].

4.4. Future Research

Future research should concentrate on long-term comparative studies of lifestyle therapies and pharmacotherapy to comprehend their sustained impact on weight reduction and metabolic health. There is a demand for more varied research populations to boost the generalizability of results across various age groups, ethnicities, and concomitant disorders. Furthermore, researching the integration of digital health technology and behavioral support systems with these therapies might give insights into enhancing patient adherence and results. Investigating the combined impact of lifestyle modifications and medicines might reveal methods for more effective and comprehensive obesity treatment.

5. Conclusion

In conclusion, our study findings have shown that lifestyle modifications and pharmacotherapy are beneficial to weight reduction and improving metabolic health in overweight and obese persons. Lifestyle modifications lead to a 5% -

10% reduction in body weight and improve metabolic indicators, including HbA1c and blood pressure [15]-[20]. Pharmacotherapy, notably with GLP-1 receptor agonists like semaglutide, may cause even more weight reduction, up to 15% of the starting body weight [15]-[20]. The treatments have different advantages and limits, with lifestyle improvements delivering wider health benefits and medication providing extra assistance for people suffering from behavioral changes only.

Authors' Contribution

All authors played several overlapping contributory roles such as conceptualization, design, cross-referencing, and fact-checking; formal analysis and interpretation of data; project administration, curation, visualization, writing—original draft, writing—review & editing; supervision, oversight, and leadership, correspondence, data curation, quality control, internal review, communications, data collection and archiving, software, literature search, validation, and approval.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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