

The Benefit of Healthy Lifestyle in the Era of New Medications to Treat Obesity

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Abstract: Incretin-based medications for treating obesity produce substantial short- and long-term weight loss and improve obesity-related comorbidities. However, associating lifestyle modification with new medications to treat obesity is generally advisable for several reasons. Firstly, healthy eating patterns and physical activity may offer important additional benefits, enhancing the patient's health and well-being. In addition, regular specialist counselling in lifestyle modification can help patients maintain their motivation levels and develop specific skills for addressing obstacles during the lengthy process of weight loss and maintenance, potentially improving outcomes in the long term. Given the high efficacy of the new weight-loss drugs, it would be timely to streamline and simplify the current gold standard of obesity management based on lifestyle modification. For example, it now seems redundant to prescribe strict diets or meal replacements to reduce calorie intake, or to recommend patients practice 200 to 300 minutes of moderate-to-vigorous-intensity exercise for enhanced weight loss. Moderate calorie restriction and, at least 150 minutes of moderate-intensity aerobic exercise and two sessions of muscle-strengthening activities per week may be more achievable and appropriate goals for sustainable weight loss in most patients on pharmaceutical obesity treatment. As regards lifestyle modification counselling, future studies should assess its optimal intensity and duration in the "new medications for obesity era".

Keywords: obesity, treatment, semaglutide, tirzepatide, GLP-1 agonists, physical activity, exercise, Mediterranean diet, weight loss, lifestyle modification

The new incretin-based drugs represent a paradigm shift in the treatment and management of obesity. Indeed, recent research shows that they are associated with significantly improved weight-loss outcomes and a substantial reduction in obesity-related comorbidities, potentially lightening the load on healthcare systems worldwide.

Semaglutide, an agonist of glucagon-like peptide-1 (GLP-1) receptor found on beta cells of the pancreas and neurons in the brain, was initially approved for better glycaemic control in type 2 diabetes. It acts through various mechanisms, including augmented insulin secretion (glucose-dependent), inhibition of glucagon release, suppression of hepatic gluconeogenesis.¹ However, the Semaglutide Treatment Effect in People with Obesity (STEP) 5 trial demonstrated that, in people with obesity or overweight and weight-related comorbidities other than diabetes, a higher dose (2.4 mg) can reduce baseline body weight by 15% for up to 2 years.² It primarily acts by modifying hunger and satiety signals in specific neural regions and delaying gastric emptying, thereby reducing energy intake.³ Similarly, 15 mg tirzepatide, which has synergistic effects on appetite, energy intake, and fat mass,⁴ by acting as a dual agonist for glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors,⁴ produced an average weight loss of 20.9% after 72 weeks in the SURMONT-1 trial.⁵

These dramatic results raise the question of whether there is still a place for traditional approaches to treating obesity. There are several good reasons for continuing to prescribe lifestyle modification and associated counselling alongside medication to treat obesity in the vast majority of patients. First and foremost, it should not be overlooked that the protocols for the STEP and SURMONT trials involved the administration of semaglutide and tirzepatide, respectively, as adjuncts to⁵ lifestyle modification. In both trials, regular lifestyle counselling sessions were delivered by a dietitian or other qualified healthcare professional to help participants adhere to a healthy, balanced diet with a moderate caloric deficit (eg, 500 kcal per day) and exercise regime (eg, at

least 150 minutes of moderate-intensity physical exercise per week).^{5,6} Behavioural strategies, such as daily recording of diet and activity using a diary or smartphone app, were also employed to this end in some cases.⁶ Hence, the overwhelmingly positive outcomes reported must be at least partially attributable to the traditional approach to obesity management.

Furthermore, the benefits of physical exercise extend beyond weight loss alone. Low cardiovascular fitness is a risk factor for cardiovascular disease and all-cause mortality.⁷ In contrast, higher levels of cardiorespiratory fitness are associated with health benefits that are independent of or enhance the effects of weight loss.⁸ In the context of weight-loss treatment with the new drugs, combining liraglutide with moderate-to-vigorous-intensity exercise elicited a more significant improvement in cardiovascular fitness than that achieved by liraglutide plus the usual activity.⁹ Weight loss does not automatically result in increased muscle strength; to this end, specific resistance exercises should be included in weight-loss treatment.¹⁰ Indeed, endurance and resistance exercises help preserve muscle mass during weight loss via traditional means,¹¹ and highly likely via the new medications as well. Finally, physical exercise improves mental health by reducing anxiety, depression, and negative mood and by improving self-esteem and cognitive function.¹² That being said, given the great efficacy of the new medications on weight loss and maintenance, the current clinical guidelines on exercise (ie, 200 to 300 min per week of moderate-to-vigorous intensity for sustainable weight loss)^{8,13} may need to be revised. Indeed, health benefits and sustained weight loss can be achieved by those taking obesity medications with the more realistic and achievable goal of at least 150 minutes of moderate-intensity aerobic activity (equivalent to a brisk walk) a week plus at least two days per week of muscle-strengthening activities.¹⁴

Similarly, prescribing diets characterized by severe caloric and nutrient restriction, as well as meal replacements, no longer appear necessary if patients are taking weight-loss drugs. Nonetheless, there are several benefits to continuing to include dietary advice in obesity management. Indeed, healthy eating patterns, such as the Mediterranean diet, have been shown to reduce the incidence of major cardiovascular events independent of weight loss.¹⁵ Moreover, several observational and interventional studies have confirmed that higher adherence to a healthy diet has beneficial effects on metabolic disorders and some types of cancers. There is also some evidence that the Mediterranean diet, in particular, is associated with a reduced risk of neurodegenerative diseases, chronic respiratory diseases, hip fractures, and depression.¹⁶ Although many diets, varying widely in macronutrient composition (ketogenic, very low-fat etc.), proposed for weight loss have been shown to produce similar improvements in terms of modest weight loss and cardiometabolic risk factor reduction, at least in the short term, the effect of the Mediterranean diet on the prevention and management of non-communicable diseases suggests that it may be preferable to other options.¹⁷ It therefore warrants investigation in conjunction with the new weight-loss drugs.

So, there are ample grounds to continue recommending lifestyle modification to patients seeking obesity treatment, even when they are taking weight-loss drugs. However, are there still valid reasons for prescribing psychological interventions, which include specific behavioural and cognitive strategies and procedures to enhance dietary and physical exercise adherence,¹⁸ such as behavioural¹⁹ or cognitive behavioural therapy (CBT) for obesity?²⁰ Are these complex interventions necessary for patients on semaglutide or tirzepatide who are following a lower-calorie diet and exercise regime to achieve and maintain long-term weight loss? Regular counselling with an obesity and lifestyle modification specialist can help patients maintain their motivation levels and develop specific skills for addressing obstacles during the process of weight loss and maintenance,²⁰ likely improving their success in the long term. However, emerging evidence raises questions about when to best intervene, how to do so, and to what extent. The Step 3 randomized clinical trial,²¹ for example, involved administration of 2.4 mg semaglutide combined with intensive behavioural therapy (ie, 30 counselling sessions) and a low-calorie diet (1000–1200 kcal/die provided as meal replacements for 8 weeks, followed by 1200–1800 kcal/die of conventional food for the remainder of the 68 weeks). Despite the intensive treatment, weight-loss outcomes were no better than those reported for the STEP 1 trial, in which 2.4 mg semaglutide was combined with a less-intensive lifestyle intervention programme (ie, 18 behavioural counselling sessions held every four weeks throughout the 68 weeks) and no initial low-calorie meal-replacement.⁶

In contrast, participants in the SURMONT-3 trial, who received intensive lifestyle modification counselling (for approximately 12 weeks) before 72 weeks of tirzepatide, appeared to lose more weight (about 25.3%)²² than those in the SURMONT-1 trial, who received lifestyle counselling throughout (20.9% at week 72).⁵ That being said, the case for sequential therapy (intensive behavioural therapy followed by medication) has been challenged by the results of the SURMONT-4 trial, in which tirzepatide without intensive lifestyle modification counselling has reportedly produced an even greater mean weight loss, 26%, after 88 weeks.²³

The findings on intensive behavioural therapy associated with the new weight loss drugs have important clinical implications and open new horizons in obesity management. Based on the available evidence, it does appear that, in combination with semaglutide or tirzepatide, less-intensive lifestyle interventions may yield similar results to intensive behavioural therapy. As the former is less costly and more easily disseminated in the real world, investigations into the optimal intensity and duration of lifestyle modification counselling in association with the new medications to treat obesity are warranted. Likewise, further studies need to be designed to confirm whether sequential therapy (ie, intensive behavioural therapy followed by medication) can have an adjuvant effect on weight loss and if specific cognitive behavioural strategies and procedures may be useful for patients taking weight-loss drugs to adopt a better healthier lifestyle, reduce attrition, and limit the typical weight regain when these drugs are suspended.²⁴

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