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Keeping the weight off

Incretin-based drugs have demonstrated unprecedented efficacy in weight-loss trials, but ensuring that healthy body weight can be maintained is fundamental to sustainable good health.

Originally developed as glucose-lowering drugs for type 2 diabetes, glucagon-like peptide-1 receptor (GLP1R) agonists are establishing new therapeutic niches, with stunning results reported in clinical trials for weight loss[1], heart failure[2] and other cardiovascular outcomes[3] in participants with and without diabetes. Generating further excitement over the past 2 years, new-generation double-hormone agonists[4] and triple-hormone agonists (with the addition of glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptor agonism, respectively) have far exceeded expectations for weight loss in people with obesity and overweight, hailing a new and unprecedented era of pharmacotherapy-meditated weight loss. These new drugs offer much-needed hope to people with obesity or overweight, many of whom have tried without success to lose weight using lifestyle interventions based on diet modification and exercise. But although the results seen in recent clinical trials are undoubtedly impressive, important questions remain about long-term use of these drugs and how to best maintain the loss once a healthy goal weight has been achieved.

More so than the initial weight loss itself, sustained weight loss — that is, achieving and maintaining a healthy body mass index — is arguably the 'holy grail' of clinical obesity management. Weight regain is all too common. A meta-analysis of long-term follow-up of studies of structured weight-loss interventions in the USA found that more the half of weight lost in the studies was regained within 2 years, with over 80% of the initial weight loss regained within 5 years[4]. Unsurprisingly, this phenomenon is not restricted only to weight loss attributable to lifestyle interventions. In the SURMOUNT-4 study, adults with obesity or overweight (but not type 2 diabetes) achieved an average weight loss of over 20% of their initial body weight when taking the dual GLP-1R–GIP agonist tirzepatide. However, after cessation of treatment, participants experienced an average weight regain of 14% over a year, compared with additional body-weight reductions of around 5% for those who remained on the treatment. These results suggest that sustained weight loss is achievable, but only with continued pharmacotherapy.

Given that semaglutide, a GLP-1R monoagonist, has already demonstrated safety and efficacy in adolescents with obesity[5] and that studies testing the safety and tolerability of tirzepatide in pediatric participants are underway, the push for pharmacotherapy as a lifelong solution to the management of obesity represents a fundamental shift in how this complex chronic condition is viewed by patients and their physicians. Adherence to lifestyle interventions is challenging for many people and therefore may not be sustainable. Metabolic surgery too can be problematic, as it is invasive and can be high risk for those with severe obesity. Embracing pharmacotherapy as an additional means of treating overweight and obesity is a step in the right direction. Yet widespread lifetime implementation of these powerful new drugs should be considered with caution.

Modern incretin-based therapies have been around for only a decade or so, and the long-term safety profiles in adults have not yet been delineated in adults, let alone in youths and children. Whether or not these drugs maintain their efficacy over decades of treatment has also not been established. Indeed, anecdotal reports of plateauing results with semaglutide are already surfacing, with consequences for adherence to treatment. In this issue of *Nature Medicine*, discussing the findings from the phase 2 program of the triple incretin agonist retatrutide, Ildiko Lingvay and Shubham Agarwal highlight the many benefits of incretin-based therapies, but also raise the need for greater understanding of the potential drug-related and weight-loss-related side effects[6].

An important, largely ignored aspect of weight loss, whether through pharmacological or lifestyle intervention, is that a portion of the weight loss comprises lean muscle. Weight regain, however, is almost entirely fat. People with chronic obesity often lose and regain weight in repeated cycles, each of which results in body-composition changes (even if they experience some net weight loss). This cycling puts people unable to sustain weight loss at risk of being metabolically less healthy than they were before the initial weight loss was achieved — in effect, at risk of developing sarcopenic obesity[7]. Commonly associated with older age and conditions such as metabolic-dysfunction-associated steatotic liver disease and cirrhosis, sarcopenic obesity driven by cycles of repeated weight loss and regain poses an additional threat to the health and well-being of people already trying to lose weight.

Sarcopenic obesity does not, however, need to be an inevitable outcome. Efforts to preserve lean muscle mass in the context of clinically meaningful weight loss are already underway. A comparison of liraglutide with and without exercise demonstrated improvements in cardiometabolic markers in the combined therapy arm, but not in the arm with liraglutide alone, despite similar levels of weight loss in each group[8]. Resistance training is widely used to prevent and treat sarcopenia in older people, which suggests that the exercise modality is probably important. Additionally, protein supplementation is being tested for lean muscle preservation in the context of dietary weight loss. A number of agents are in development for the treatment of sarcopenia[9], some of which could be repurposed for the maintenance of muscle mass and integrity in people being treated with incretin-based therapies. Measuring changes in body composition in trials is fundamental to understanding how and if such interventions for weight loss and sarcopenia are truly effective.

New-generation incretin-based therapies are powerful tools with enormous potential to change the course of the global obesity epidemic, as well as the treatment landscape for other cardiometabolic diseases. But patients and physicians must not slide into believing the fallacy that pharmacotherapy-mediated weight loss is a 'silver bullet' for better health. These game-changing drugs should not necessarily be initiated with lifelong therapy as the goal. Instead, anti-obesity medications should be added to the armory of weight-loss interventions, alongside diet and exercise, to help patients lose weight safely and sustainably.

Editorial

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