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## Weight regain after cessation of GLP-1 drugs

Weight management drugs are no magic bullets for treating obesity

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Obesity is one of the major public health and clinical concerns globally, including in industrialised countries, as well as lower middle income countries such as India and Egypt. For example, the prevalence of obesity among adults has reached 40.3% in the US<sup>1</sup> and 26.2% in the UK.<sup>2</sup> Obesity and excess weight gain predispose people to an increased risk of developing numerous chronic diseases, including type 2 diabetes, cardiovascular conditions, and certain types of cancer, along with decline in cognitive function, dementia, and premature death.<sup>3</sup>

Unfortunately, obesity is not a disease that can be easily treated and managed. Numerous dietary and lifestyle modifications are recommended to help clinicians manage this condition in patients. It is, however, well known that the effects vary among individuals, and weight regain is almost inevitable for most people who initially lose weight. Procedures such as bariatric surgery seem to be more effective in achieving substantial, sustained weight loss, although the invasive nature of such surgeries and other concerns limit their application for the treatment of obesity.<sup>4</sup>

More recently, medications such as glucagon-like peptide-1 (GLP-1) receptor agonists have gained popularity as the preferred drug treatments for obesity and related conditions. The efficacy of these medications has been demonstrated in clinical trials, which collectively showed that, on average, the use of GLP-1 receptor agonists may lead to a 4.6 kg weight loss or >2 unit reduction of body mass index.<sup>5</sup> Although the efficacy of these medications is highly encouraging, the consequences of the cessation of treatment have not been previously systematically reviewed, until the linked systematic review and meta-analysis by West and colleagues (doi:10.1136/bmj-2025-085304).<sup>6</sup> This is a timely investigation because, as the authors pointed out, real world observations suggested that a large proportion of people would discontinue use of a GLP-1 receptor agonist within 12 months of initiation.<sup>7</sup> The results from West and colleagues' meta-analysis indicated that, after an average of 39 weeks' treatment, cessation led to 0.4 kg/month weight regain, resulting in a body weight that would return to baseline values in less than two years.

The results are not surprising given that it is well documented that reduced adherence to, or cessation of, dietary and lifestyle interventions leads to similar patterns of weight regain. Nevertheless, the study findings casted doubt on the notion that GLP-1 receptor agonists are a perfect cure for obesity. Issues such as high costs, side effects, and the inconvenience of injections are among some common reasons for discontinuing the medications.<sup>7,8</sup> How

shall we deal with the weight regain after treatment is discontinued? One strategy is perhaps to switch to healthy diets and healthy lifestyles that have been robustly and consistently proven to be effective in preventing excess weight regain in observational studies with extended follow-up,<sup>9</sup> although further research is needed to study weight regain in individuals who adopt a healthier lifestyle after the cessation of GLP-1 receptor agonists.

Considerable weight loss, even if followed by weight regain, can still lead to beneficial long term consequences for people living with obesity.<sup>10</sup> Participants in the Diabetes Prevention Program trial achieved 5-7% weight loss through a structured healthy lifestyle intervention.<sup>11</sup> Even though the lifestyle intervention group eventually regained weight, the cumulative incidence of developing diabetes was lower in the lifestyle intervention group compared with placebo group. In observational studies, individuals with obesity who intentionally lost ≥4.5 kg of body weight through various strategies, ranging from dietary modifications to commercial weight loss programmes, had a statistically significantly lower incidence of diabetes than their counterparts without weight loss attempts.<sup>12</sup> One caveat, however, is that individuals in the healthy body mass index range (18.5-24.9), when intentionally losing weight through these strategies (except for exercise), had an increased risk of developing diabetes compared with their counterparts who did not seek to lose weight. This phenomenon is probably due to the mechanism of "fat overshooting," whereby individuals with a healthy body mass index lose more lean mass than people with obesity and, upon regaining weight, experience a faster increase in fat mass than lean mass.<sup>13</sup>

GLP-1 receptor agonists should not be relied on as a magic cure for treating obesity. While considerable weight loss, even if temporary, may still bring some health benefits for those with obesity, people using GLP-1 receptor agonists should be aware of the high discontinuation rate and the consequences of cessation of medications. Healthy dietary and lifestyle practises should remain the foundation for obesity treatment and management, with medications such as GLP-1 receptor agonists used as adjuncts. Such practises not only help prevent excess weight gain but can also lead to numerous health benefits that go beyond weight control. Effective public health measures, such as taxation on sugary beverages, clear food labelling, and subsidies for fresh fruit and vegetables, should be in place to facilitate the adherence and improvement of diet quality.

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