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Reappraising obesity management in the GLP-1 receptor agonist era

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Incretin-based therapies are increasingly used for obesity management, raising debate about whether they could challenge or replace metabolic bariatric surgery (MBS). Here, we compare evidence for both treatments, focusing on effectiveness, limitations and costs. We also explore how obesity care pathways may evolve and highlight key evidence gaps that must be addressed to define the future roles of incretin-based therapies and MBS in obesity management.

Obesity is a multisystem chronic disease that increases the risk of cardiovascular disease, type 2 diabetes, hypertension, dyslipidaemia and several cancers. It is also a growing global public health concern; by 2030 it is expected that 1.1 billion adults will be living with obesity worldwide[1]. Management options centre on lifestyle optimisation, MBS and pharmacotherapy. Until recently, medication options were limited, and MBS is historically the treatment modality associated with the greatest and most durable weight loss, as well as superior long-term outcomes, compared to medication or lifestyle interventions alone. However, substantial advances in incretin-based therapies have reshaped the treatment landscape. These include semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA) and tirzepatide, a combined GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. For ease, we will refer to both as GLP-1RA.

The principal action of GLP-1RA is to mimic glucagon-like peptide-1 (GLP-1), a gut hormone which is released by enteroendocrine cells in response to gut luminal nutrient sensing after eating. GLP-1 stimulates insulin secretion and suppresses appetite by delaying gastric emptying and signalling to the brain (directly via the hypothalamus and brainstem; indirectly via activation of portal vein vagal afferents) to increase satiety[2]. GLP-1RA are a well-established treatment option for type 2 diabetes in adults and are now licensed for obesity management. In the STEP-1 trial[3] published in 2021, patients who had a BMI of 30 or greater (or ≥27 with ≥1 weight-related coexisting condition) who received semaglutide, plus lifestyle intervention, lost, on average, 14.9% of their bodyweight from baseline at 68 weeks of treatment. This encouraging finding indicated that GLP1-RA therapy could enable a meaningful degree of weight loss, with the added benefits of being non-invasive, adjustable to patients' needs, and deliverable in routine outpatient care. The SELECT trial, published in 2023, investigated whether treatment with semaglutide could reduce the cardiovascular risk in people with obesity or overweight without type 2 diabetes, but with proven cardiovascular disease[4]. It found that participants taking semaglutide over an average follow-up time of 40 months were 20% less likely to have a primary cardiovascular event compared to participants who took placebo, despite a modest mean weight loss of 9.4% with semaglutide. These trial results indicate that treatment with GLP-1 RA attenuates the cardiovascular risk in patients with overweight or obesity, showcasing its potential as a disease-modifying treatment in obesity.

There have also been encouraging results from clinical trials of tirzepatide. Like GLP-1, GIP stimulates insulin release, but in addition it also modulates adipose tissue function and fatty acid metabolism. The SURMOUNT-1 trial, published in 2022, found participants with an average BMI of 38, without type 2 diabetes, lost an average of 20.9% of their bodyweight when they took tirzepatide 15 mg weekly, 19.5% with tirzepatide 10 mg weekly and 15.0% with tirzepatide 5 mg weekly, over 72 weeks[5]. These results show that tirzepatide can enable substantial, dose-dependent weight loss in individuals with obesity without diabetes. A head-to-head trial of tirzepatide vs semaglutide showed that on average, tirzepatide is associated with 6% more weight loss than semaglutide at current obesity-indication doses for both drugs[6]. Furthermore, the magnitude of weight-loss with tirzepatide approaches outcomes typically associated with MBS. Evidence of tirzepatide's effect on cardiovascular outcomes will come with the SURMOUNT-MMO trial results, which are likely to be reported in 2027.

Further developments in the pharmacotherapy domain promise to deliver better and more accessible weight loss for patients. Retatrutide, a 'triple-agonist' of GLP-1, GIP and glucagon receptors, has recently been reported to deliver a headline 28.7% mean weight loss at the highest dose in Phase III trials[7]. Oral agents such as semaglutide (co-formulated with a gastric absorption enhancer)[8] or orforglipron[9], a small-molecule GLP-1RA, also promise to expand access to these agents by enabling treatment of patients who do not wish to or cannot inject themselves. These oral agents are not as dependent on a 'cold chain' for distribution and storage, unlike the injectable agents used so far, and will be easier to deliver globally.

Although clinical trials of incretin-based therapies have shown highly encouraging results, important limitations and challenges remain. Firstly, the weight-loss effects achieved with incretin-based therapy diminish once treatment is discontinued. In an extension analysis of 327 participants from the STEP-1 trial[10], in whom the mean weight loss with semaglutide was 17.3%, participants regained approximately two-thirds of the weight (about 11.6 percentage points) 52 weeks after cessation, resulting in a net loss of only ~5.6% from baseline. In addition, most cardiometabolic improvements, including reductions in blood pressure, cholesterol and HbA1c, drifted back toward baseline.

Furthermore, there is a lack of evidence regarding the long-term effectiveness and safety of incretin-based therapy. Most clinical trials evaluating semaglutide and tirzepatide for overweight and obesity have followed participants for only two to three years, with the most commonly reported adverse events being gastrointestinal upset (nausea, vomiting, diarrhoea). More rarely, pancreatitis was also reported[3,5]. Although a growing body of

evidence supports the effectiveness of GLP-1 RA over this modest time frame, obesity is a chronic disease and treatment must similarly be sustained. Hence, there is a critical need for long-term data to determine whether these therapies can safely sustain weight loss over many years.

On the other hand, the long-term effects of MBS on weight loss and mortality are well established. The prospective, controlled Swedish Obesity Subjects (SOS) study followed participants for up to 20 years after MBS, of whom 13% underwent gastric bypass, 19% underwent banding and 68% underwent vertical banded gastroplasty. Sustained weight loss was observed throughout follow-up: mean reductions of 23%, 17%, 16% and 18% were reported at 2, 10, 15 and 20 years respectively. In addition, MBS was associated with a reduced incidence of myocardial infarction, stroke, type 2 diabetes and cancer, as well as a long-term reduction in overall mortality[11].

Weight-loss outcomes vary by surgical procedure. A recent UK randomised controlled trial found that Roux-en-Y gastric bypass facilitated the greatest weight loss (26.8%), followed by sleeve gastrectomy (19.4%) and gastric banding (14.0%)[12]. These results remain superior to the weight-loss outcomes achieved with GLP-1 RA therapy at present, although newer therapies such as retatrutide may well provide similar magnitudes of weight loss (see above). However, MBS has limitations related to the capacity of surgeons and facilities, and inherent risks of undergoing surgery, although these are rare. There is also the potential for complex long-term complications, such as chronic abdominal pain, malnutrition, post-bariatric hypoglycaemia and dumping syndrome[13].

Head-to-head comparisons between MBS and treatment with GLP-1 RA therapy exist, but are limited as most evaluate older GLP-1RA used for type 2 diabetes mellitus, rather than the newer, higher dose formulations developed for obesity treatment. An observational study conducted in the United States compared macrovascular and microvascular outcomes among patients with type 2 diabetes and obesity treated with metabolic surgery versus GLP-1RA therapy between 2010 and 2017. Surgery was associated with a 32% lower risk of all-cause mortality. However, GLP-1RA exposure in this cohort was heterogeneous, and only a minority of patients received semaglutide (26.5%) and tirzepatide (4.4%), likely at the lower doses used for diabetes management, rather than the obesity-specific regimens[14].

A recent network meta-analysis of randomised controlled trials compared 12 studies evaluating MBS (sleeve gastrectomy and Roux-en-Y gastric bypass) and 18 trials evaluating pharmacological interventions; semaglutide, tirzepatide and liraglutide (another GLP-1 RA) at doses used for obesity management. Overall, MBS was associated with greater reductions in body weight and greater improvements in HbA1c. However, in the tirzepatide-specific subgroup analysis, no significant difference in weight loss was observed between tirzepatide and MBS, suggesting tirzepatide may be approaching the efficacy of MBS interventions. Importantly, all comparisons between MBS and GLP-1RA in this meta-analysis were indirect, as no direct head-to-head trials are currently available[15].

Both MBS and GLP-1RA therapy have been found to be cost-effective by the UK National Institute for Health and Care Excellence, due to the reduced health costs, improved lifespan and improvements in quality of life associated with weight loss and reduced co-morbidities. From a health-economic perspective, MBS is associated with substantial upfront costs but is cost-effective in the long-term due to durable weight loss and reductions in obesity complications. In contrast, GLP-1RA therapy incurs ongoing, potentially lifelong costs that are highly dependent on drug pricing and treatment duration. These findings were echoed in a retrospective cohort study, performed by Barrett et al., which analysed data from a US health insurance claims database comparing MBS with GLP-1 RA between 2018 and 2023. Within the US cohort, 45% of the GLP-RA cohort received semaglutide and 11% received tirzepatide. During the first year of treatment, the mean total monthly cost was higher for patients undergoing MBS than for those receiving GLP-1RA (US$3161.49 vs $2841.83). In contrast, in the second year, mean monthly costs were higher in the GLP-1RA group compared with the MBS group ($2448.42 vs $1154.68)[16]. Although this retrospective analysis suggests that MBS appears more cost-effective compared with GLP-1RA, we must acknowledge that retrospective analyses suffer from the fact that they inherently reflect previous practice, as well as unaccounted biases. In addition, the costs of GLP-1RA and surgery in the US are far higher than the respective costs in other countries (for example, tirzepatide costs approximately US$1100 per month in the US, vs $520 in the UK), so the conclusions derived from US-based data may not be valid for other contexts.

Obesity is a chronic and relapsing disease that requires lifelong monitoring. Based on current evidence and emerging clinical practice, it is likely that treatment approaches will become increasingly stratified and personalised according to the severity of obesity and associated comorbidities. For individuals with the highest levels of obesity, the most effective strategy may involve pre-treatment with GLP-1RA to facilitate subsequent MBS, thereby maximising the potential for sustained weight loss and improvement in obesity-related comorbidities.

The recent development of GLP-1RA for obesity has introduced a non-invasive and adaptable treatment option, capable of achieving clinically meaningful weight loss. These therapies are likely to complement, rather than replace, MBS in the management of obesity. However, important limitations remain; long-term effectiveness and safety have yet to be fully established, and weight loss can reverse following treatment discontinuation. Only a definitive randomised controlled trial comparing GLP-1RA therapy with MBS will provide the information required to inform clinicians and patients on the optimal choice for obesity management.

Data availability

No datasets were generated or analysed during the current study.

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References

1. World Obesity Federation. World Obesity Atlas 2025 [Internet]. London: World Obesity Federation. https://data.worldobesity.org/publications/world-obesity-atlas-2025-v6.pdf (2025).
2. Drucker, D. J. & Nauck, M. A. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **368**, 1696–1705 (2006).
3. Wilding, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **384**, 989–1002 (2021).
4. Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
5. Jastreboff, A. M. et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* **387**, 205–216 (2022).
6. Aronne, L. J. et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N. Engl. J. Med.* **393**, 26–36 (2025).
7. Eli Lilly and Company. Lilly's triple agonist, retatrutide, delivered weight loss of up to an average of 71.2 lbs along with substantial relief from osteoarthritis pain in first successful Phase 3 trial [press release on the Internet]. PR Newswire. https://www.prnewswire.com/news-releases/lillys-triple-agonist-retatrutide-delivered-weight-loss-of-up-to-an-average-of-71-2-lbs-along-with-substantial-relief-from-osteoarthritis-pain-in-first-successful-phase-3-trial-302638804.html (2025).

8. Wharton, S. et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N. Engl. J. Med.* **393**, 1077–1087 (2025).
9. Wharton, S. et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N. Engl. J. Med.* **393**, 1796–1806 (2025).
10. Wilding, J. P. H. et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diab. Obes. Metab.* **24**, 1553–1564 (2022).
11. Sjöström, L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J. Intern. Med.* **273**, 219–234 (2013).
12. Abbott et al. Roux-en-Y gastric bypass, adjustable gastric banding, or sleeve gastrectomy for severe obesity (By-Band-Sleeve): a multicentre, open label, three-group, randomised controlled trial. *Lancet Diab. Endocrinol.* **13**, 410–426 (2025).
13. Hazlehurst, J. et al. Society for endocrinology guidelines for the diagnosis and management of post-bariatric hypoglycaemia. *Endocr. Connect* **13**, e230285 (2024).
14. Gasoyan, H. et al. Macrovascular and microvascular outcomes of metabolic surgery versus GLP-1 receptor agonists in patients with diabetes and obesity. *Nat. Med.* **31**, 3341–3349 (2025).
15. Sabatella, L. et al. Comparative efficacy of metabolic/bariatric surgery versus GLP-1 receptor agonists: a network meta-analysis of randomized controlled trials. *Obesity* **34**, 770–781 (2026).
16. Barrett, T. S., Hafermann, J. O., Richards, S., LeJeune, K. & Eid, G. M. Obesity treatment with bariatric surgery vs GLP-1 receptor agonists. *JAMA Surg.* **160**, 1232–1239 (2025).

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T.M-M. Tan is a former shareholder in, consultant for and founder of Zihipp Ltd. Currently serving in advisory boards for Nxera and Amylyx. T. Christmas and A.R. Ahmed have no conflicts of interest.

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