Treating obesity is no longer inSURMOUNTable

The SURMOUNT-2 trial was simultaneously presented at the ADA 2023 Scientific Sessions and published in the *Lancet*, and demonstrated that use of the dual GLP-1/GIP receptor agonist tirzepatide resulted in a mean body weight reduction of up to 14.7% after 72 weeks in people living with type 2 diabetes and comorbid obesity or excess weight. This level of weight loss has previously been associated with type 2 diabetes remission, and was also accompanied by clinically meaningful improvements in a number of cardiometabolic risk factors, including lipids, blood pressure and liver enzymes. With tirzepatide and semaglutide, we now have two compelling evidence-based pharmacological therapies with superior efficacy and safety profiles compared to previous obesity medications. However, there remains uncertainty about durability of effect and impact of withdrawal of treatment on weight loss maintenance. Amid calls to use percentage weight loss as a target biomarker in obesity (like HbA_{1c} in diabetes, LDL-cholesterol in atherosclerotic cardiovascular disease and albuminuria in chronic kidney disease), a seismic shift in how we approach the management of obesity, with significant financial implications for healthcare systems globally, may be required.

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The SURMOUNT-2 trial was simultaneously presented at the ADA 2023 Scientific Sessions in San Diego and published in the *Lancet*. The trial demonstrated that use of the dual GLP-1 and GIP receptor agonist tirzepatide resulted in a mean body weight reduction of up to 14.7% after 72 weeks in people living with type 2 diabetes and comorbid obesity or excess weight.

Moreover, around one third of participants lost over 20% of their baseline body weight. The average weight reduction with tirzepatide after 72 weeks was 14–16 kg, a level that has previously been associated with remission of type 2 diabetes (Lean et al, 2018).

With respect to glucose-lowering efficacy (a pre-specified key secondary endpoint of the trial), use of tirzepatide reduced HbA_{1c} by 23 mmol/mol (2.1%) after 72 weeks. The mean HbA_{1c} of trial participants at trial end was 41 mmol/mol (5.9%), reflecting, in other words, normalisation of glucose levels.

Additional benefits observed included reductions in fasting glucose and insulin levels (indicating a significant increase in insulin sensitivity); improvements in lipid profile, particularly fasting triglyceride and non-HDL cholesterol levels; a reduction in systolic blood pressure of 6–7 mmHg; and reductions in liver enzymes (notably a 35% improvement in ALT) – all clinically meaningful improvements in cardiometabolic risk factors.

SURMOUNT-2 also explored the safety profile of tirzepatide; reassuringly, the overall rate of serious adverse events was similar between the tirzepatide and placebo groups. Most treatment-emergent adverse effects with tirzepatide were, predictably, gastrointestinal in nature: most commonly nausea, diarrhoea and vomiting. However, these gastrointestinal adverse effects occurred primarily during the dose escalation period, were mostly mild to moderate in severity and decreased over time.

Importantly, there was no imbalance observed with diabetic retinopathy events, liver and gallbladder events, malignancies (including pancreatic cancer and medullary thyroid cancer) and pancreatitis, which have previously shadowed certain incretin molecules. There were also no cases of severe hypoglycaemia

Citation: Fernando K (2023) Diabetes Distilled: Treating obesity is no longer inSURMOUNTable. *Diabetes & Primary Care* **25**: 133–5

"Percentage weight loss should now be used as a target biomarker in obesity (like HbA_{1c} in diabetes, LDL-cholesterol in atherosclerotic cardiovascular disease and albuminuria in chronic kidney disease) to mitigate the specific complications of obesity."

detected, despite the potent glucose-lowering efficacy of tirzepatide. Mean pancreatic enzyme levels were increased but remained within the normal range, which is consistent with other incretin therapies used for obesity, such as semaglutide. Overall, mean pulse rate increased by 1 bpm over 72 weeks; there was an initial rise of 4 bpm observed, which subsequently decreased.

A seismic shift is required

It is well known that people living with obesity and type 2 diabetes lose less weight than those living with obesity alone, so SURMOUNT-2 is a prodigious advance for the management of obesity and type 2 diabetes. The results of SURMOUNT-2 also surpass the compelling results with semaglutide 2.4 mg in the STEP-2 trial (Davies et al, 2021).

Obesity is now recognised as a chronic disease with multiple pathophysiological aspects; it involves more than just an increase in body mass. Like other chronic diseases, obesity is relapsing in nature and can lead to a range of complications, including cardiometabolic disease and malignancy.

Different complications require different amounts of weight loss for treatment; for example, in non-alcoholic fatty liver disease (NAFLD), 3–5% weight loss reduces hepatic steatosis, while ≥5–7% weight loss can lead to resolution of non-alcoholic steatophepatitis and ≥10% weight loss improves hepatic fibrosis (Hannah and Harrison, 2016). The 2022 ADA/EASD Consensus Report suggests that 5–10% weight loss confers metabolic improvement in type 2 diabetes, and weight loss of >10–15% can lead to remission of type 2 diabetes (Davies et al, 2022).

Percentage weight loss should now be used as a target biomarker in obesity (like HbA_{1c} in diabetes, LDL-cholesterol in atherosclerotic cardiovascular disease and albuminuria in chronic kidney disease) to mitigate the specific complications of obesity (Garvey, 2022).

Much of current thinking for preventing and treating obesity centres around hedonic eating in combination with a sedentary lifestyle; "Eat less, move more" is commonly delivered advice to people living with obesity. However, while these are contributing factors, it is well known that pathophysiological mechanisms affecting appetite and satiety are pivotal in the development of obesity. Optimising satiety needs to be addressed early in the management of obesity, as calorie restriction alone is unlikely to be a long-term solution if there is ongoing abnormal hunger.

A seismic shift is required in how we approach the management of obesity, with increased access to weight management services and evidence-based pharmacological therapies that directly impact appetite and satiety, such as semaglutide and tirzepatide.

Ongoing questions

As with all good studies, SURMOUNT-2 raises more questions than answers. What is the durability of effect of tirzepatide after 72 weeks and, crucially, what is the effect of withdrawal of tirzepatide on weight loss maintenance? The STEP-4 weight maintenance trial and STEP-1 off-treatment extension study both demonstrated weight regain after discontinuation of semaglutide, suggesting that incretin therapy is required over the long term for sustained weight loss (Rubino et al, 2021; Wilding et al, 2022). This has significant financial implications for healthcare systems globally. One solution would be a phased approach to the management of obesity, with early phases using highly efficacious obesity drugs such as tirzepatide or semaglutide and then transitioning to lower-efficacy and cheaper obesity drugs for weight maintenance. Several such obesity maintenance drugs are in the early stages of development.

This approach is analogous to the treatment of rheumatoid arthritis, where often potent targeted biological therapy is used early on to achieve remission of arthritis, followed by a switch to a conventional DMARD for maintenance therapy, for reasons of long-term safety and health economics. Using this approach for obesity management might help the sustainability of healthcare systems.

Finally, what are the cardiovascular, renal and liver benefits of tirzepatide? These questions will

hopefully be answered on completion of the SURPASS-CVOT, SURMOUNT-MMO and SYNERGY-NASH trials, which, unfortunately, are not due to report soon. However, positive results would facilitate targeted use of tirzepatide for people living with obesity and specific co-morbidities such as atherosclerotic cardiovascular disease, chronic kidney disease and NAFLD.

In conclusion, treatment of obesity is no longer insurmountable, with two compelling evidence-based pharmacological therapies with superior efficacy and safety profiles compared to previous obesity medications. However, there remains uncertainty about durability of effect and impact of withdrawal of treatment on weight loss maintenance. Much-needed real-world data will help resolve some of this uncertainty. ■

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Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

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