New approaches to weight loss and glycaemic control in T2DM, focusing on tirzepatide and newer agents

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Introduction

The incidence of type 2 diabetes mellitus (T2DM) and obesity are increasing rapidly in both the developed and developing world due to unhealthy dietary habits and sedentary lifestyles. Obesity and diabetes are associated with substantial increases in morbidity, premature mortality, impaired quality of life and large healthcare costs. People with obesity are at higher risk of developing diabetes compared to those at a healthy weight and the treatment of T2DM in people with obesity is challenging due to insulin resistance. Weight loss improves insulin sensitivity, leading to better glycaemic control. The treatment of obesity includes lifestyle intervention, pharmacotherapeutics and bariatric surgery. Lifestyle changes alone do not produce marked or sustained weight loss. Bariatric surgery is more effective in terms of weight loss but is associated with perioperative mortality and surgical complications. Pharmacotherapeutics are an alternative strategy to reduce body weight.

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has opened a new avenue for glucose-lowering therapy in people with obesity and T2DM and for the treatment of obesity in people without diabetes.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the L-cells of the ileum and colon in response to food intake. It promotes release of insulin, decreases glucagon secretion and slows down gastric emptying. GLP-1 receptors are also found in the satiety centre of the brain, leading to decreased food intake, and they also modulate fat utilisation. GLP-1 is cleared by the enzyme dipeptidyl peptidase 4 (DPP4) and the incretin effect is known to be reduced in people with T2DM.[1] GLP-1 RAs are resistant to the actions of DPP4, so they have a long circulatory half-life and their impact on weight is not dependent on the presence of hyperglycaemia (in contrast with sodium glucose co-transporter 2 inhibitors). GLP-1 RAs also reduce cardiovascular risk: multiple experimental and clinical trials have shown ~15% reduction of major adverse cardiovascular events in people with diabetes.[2] As a result, GLP-1 RAs are recommended in the treatment of patients with T2DM and established cardiovascular disease and those at high risk.

People with diabetes achieved clinically significant weight loss with GLP-1 RAs. This led to further research into their use for weight loss. We discuss those GLP-1 RAs which are approved in the treatment of diabetes and weight loss in this review.

Since the approval of the first GLP-1 RA, exenatide, a number of agents have been approved for treatment of T2DM. Two are now licensed for weight management. Dual agonists of the receptors for GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the most recently licensed group of glucose-lowering therapies. Tirzepatide was the first dual agonist to be approved in Europe, in 2022. This recently received NICE approval for glucose lowering and has European Medicines Agency (EMA) approval for weight loss (both in 2023).

Liraglutide

Liraglutide is an analogue which is structurally similar to human GLP-1, with 97% homology for amino acid residues. In the phase III clinical trial programme, investigating treatment with liraglutide 1.2 and 1.8 mg as monotherapy and in combination with other oral antidiabetic drugs, the mean reduction of haemoglobin A1c (HbA_{1c}) was 5 to 7.5 mmol/mol and a clinically significant reduction in fasting and postprandial glucose was observed.[3]

A systematic review of real-world clinical effectiveness of liraglutide reported a mean change in HbA_{1c} from baseline of -0.45 to -11 mmol/mol and absolute weight from baseline of -1.3 to -8.65 kg.[4]

Further studies with high-dose liraglutide 3 mg OD demonstrated >5% body weight reduction.[5] Along with its peripheral actions, liraglutide stimulates appetite-inhibiting neurons and inhibits appetite-stimulating neurons in the hypothalamus, resulting in a reduction in hunger and an increase in the sensation of fullness.[5] In the phase III clinical trial programme in people with obesity/overweight either alone or with co-morbidities, at week 56, 63.2% of the participants in the liraglutide group had lost at least 5% of the body weight, compared with 27.1% in the placebo group. Furthermore, 33.1% of participants in the liraglutide group had lost more than 10% of the body weight compared to 10.6% in the placebo group.[6] Liraglutide 3 mg along with diet and exercise has been shown

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to reduce 6.5% of the body weight at the end of six months in a real-world setting.[7] In comparison, a meta-analysis of randomised controlled trials of lifestyle interventions showed an average weight loss of < 5% (3.63 kg at one year and 2.45 kg at three years), with slightly greater weight loss in obese and very obese people compared to those who were overweight.[8]

Liraglutide 1.2 mg was initially approved for the treatment of T2DM in 2010 in the UK and the 3.0 mg dose was approved for the management of overweight and obesity in 2020.

Semaglutide

This is a long-acting GLP-1 RA which has 94% sequence homology with native GLP-1. The SUSTAIN 1 to 5 trials demonstrated a mean HbA_{1c} reduction of 6 to 7.5 mmol/mol with semaglutide 0.5 mg and 9.3 to 11.1 mmol/mol with semaglutide 1.0 mg compared to a reduction of 0.1 to 4.5 mmol/mol with other hypoglycaemic agents. Greater weight loss was also observed in the semaglutide group.[9] In the real-world population, treatment with semaglutide has led to clinically significant improvements in glycaemic control.[10]

The STEP programme of clinical trials studied the effect of high-dose semaglutide 2.4 mg weekly (QW) injection in people with overweight/obesity. In each of the STEP 1 to 4 placebo-controlled trials, the mean change in body weight from baseline in the semaglutide group was -9.6% to -17.4%.[11-14] The change was -15.2% in the STEP 5 trial,[15] and 83% of the participants who received semaglutide 2.4 mg QW achieved 5% or greater weight loss in the STEP 6 trial.[16] In the STEP 8 trial, mean body weight change from baseline to 68 weeks was -15.8% with semaglutide 2.4 mg QW versus -6.4% with liraglutide 3 mg OD.[17]

In a retrospective analysis of 175 people with overweight or obesity who received semaglutide 1.7 mg or 2.4 mg QW in a routine clinical setting, the mean weight loss was 5.9% at three months. Of the 102 individuals followed for six months, 87% achieved at least 5% weight loss.[18]

Once-weekly semaglutide was approved in the UK for the treatment of T2DM in 2019 and the 2.4 mg dose for the treatment of obesity was approved in 2023.

Tirzepatide 5 mg, 10 mg and 15 mg weekly

Tirzepatide is a long-acting peptide which has agonist activity at both the GLP-1 and GIP receptors. GIP is secreted from the K-cells of the small intestine in response to the ingestion of food and increases insulin secretion. GIP agonism appears to increase the appetite suppression of GLP-1 receptor agonists as well as further enhancing prandial insulin secretion. In contrast to GLP-1 agonism, it increases glucagon secretion and favourably influences insulin resistance and lipid metabolism. *In vitro* and *in vivo* studies have demonstrated better glycaemic control and weight loss through synergistic actions of GLP-1/GIP compared to separate administration of either peptide. Subsequently, potent glucose-lowering and weight loss effects were confirmed in the tirzepatide group in phase III clinical trials.[19]

The SURPASS studies have examined the glucose-lowering effect of tirzepatide in T2DM. The SURPASS programme showed excellent glucose lowering across the T2DM spectrum from monotherapy to addition of insulin; 86-92% of participants achieved an HbA_{1c} ≤48 mmol/mol on the highest dose of 15 mg QW. The results were superior to active treatment with both insulin degludec and subcutaneous semaglutide 1mg QW.[20,21] The secondary end-point in the SURPASS studies of people with T2DM was weight reduction, and 27-43% of participants on the higher dose lost ≥15% of their body weight.

Tirzepatide was approved as a glucose-lowering therapy by the EMA in September 2022 and in the UK in 2023. The National Institute for Health and Care Excellence (NICE) UK recommends tirzepatide for treating T2DM alongside diet and exercise in adults when the diabetes is insufficiently controlled; only if triple therapy with metformin and two other oral antidiabetic drugs is ineffective, not tolerated or contraindicated; and they have a body mass index (BMI) of 35 kg/m^2 or more and specific psychological or other medical problems associated with obesity, or they have a BMI of less than 35 kg/m^2 and insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related complications. Lower BMI thresholds (usually reduced by 2.5 kg/m^2) are recommended for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

The SURMOUNT 1-4 studies have specifically addressed the weight-lowering effect of tirzepatide. In the SURMOUNT-1 trial, the mean percentage weight reduction from baseline to 72 weeks with tirzepatide 15 mg QW was 20.9%;[22] it was -12.8% and -14.7% with tirzepatide 10 mg and 15 mg in SURMOUNT 2;[23] and -18.4% in the SURMOUNT 3 trial.[24] In SURMOUNT 4, a mean weight reduction of 20.9% was achieved at 36 weeks with tirzepatide 10 or 15 mg QW. At 88 weeks, 89% of the participants who continued with tirzepatide maintained 80% of their weight loss compared to 16% in those who switched to placebo at week 36.[25] Participants without T2DM did better in terms of weight loss in the SURMOUNT studies. The reason for this remains unclear (but has been seen with other agents investigated for weight loss). Tirzepatide was approved for the treatment of obesity in 2023 in both the US and EU.

Emerging therapeutics

The OASIS 1 trial assessed the safety and efficacy of oral semaglutide 50 mg OD versus placebo in people with overweight or obesity without T2DM. It reported a superior and clinically meaningful weight reduction, with 85% of the participants achieving weight loss of at least 5% compared to placebo.[26] Oral semaglutide is not yet licensed for weight reduction.

Other emerging therapeutics are CagriSema, a combination of subcutaneous cagrilinitide (a long-acting amylin analogue) and semaglutide; the oral small molecule (i.e. non-peptide) GLP-1 RAs danugliprone and orforglipron; GLP-1 RA and glucagon dual agonists (e.g. survodutide); and triple GLP-1/GIP/glucagon (GCK) agonists, the first of which is retatrutide.

In summary

Recent advances in glucose-lowering therapies have enabled

the possibility of achieving clinically meaningful weight loss with concurrent improvement in other metabolic parameters, as well as health-related quality of life. The dual GLP-1/GIP agonist tirzepatide has been shown to be more effective in reducing weight in comparison to other agents so far launched. The early use of these medicines for treatment of T2DM is likely to increase significantly in the future.

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