The twincretin tirzepatide – a promising treatment for NAFLD

Non-alcoholic fatty liver disease (NAFLD) is closely associated with type 2 diabetes and is an independent predictor of all-cause mortality. It is one of the fastest-growing indications for liver transplantation in the Western world. In the present study, the authors evaluated the effects of the dual GIP/GLP-1 receptor agonist tirzepatide on liver fat content in people with type 2 diabetes and significant NAFLD. In pooled analysis, tirzepatide 10 mg and 15 mg were found to reduce liver fat content by more than half (by 8.09%, from a baseline of 15.71%) after 1 year of treatment. The active comparator, insulin degludec, reduced fat levels by 3.38%. These results position tirzepatide as a promising future treatment for NAFLD.

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Tirzepatide is a novel, once-weekly, dual GIP and GLP-1 receptor agonist ("twincretin") for the treatment of type 2 diabetes. GIP (glucose-dependent insulinotropic polypeptide) is another incretin hormone that, when targeted alongside GLP-1, complements the known benefits of GLP-1 receptor agonists, resulting in greater effects on blood glucose and body weight. Tirzepatide will be commercially available during 2023.

The SURPASS and SURMOUNT trial programme investigated the effects of tirzepatide at doses of 5, 10 and 15 mg in a range of clinical scenarios (people with and without type 2 diabetes), against placebo or an active comparator.

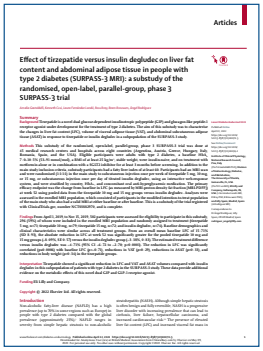
SURPASS-3 compared the effect of weekly tirzepatide against titrated daily insulin degludec in people living with type 2 diabetes taking metformin with or without an SGLT2 inhibitor (Ludvik et al, 2021). Those taking tirzepatide 15 mg weekly achieved a 26 mmol/mol (2.37%) average reduction in HbA_{1c} after 52 weeks of treatment, compared with a 15 mmol/mol (1.34%) reduction with insulin degludec. Furthermore, the tirzepatide groups lost an average of 7.5, 10.7 and 12.9 kg of body weight, respectively, compared with a weight gain of 2.3 kg with insulin degludec. There was also significantly less hypoglycaemia observed with tirzepatide. The most common adverse events in tirzepatide-treated individuals were mild-to-moderate gastrointestinal symptoms, which reduced over time. The safety profile of tirzepatide was similar to that of GLP-1 receptor agonists.

The SURPASS-3 MRI substudy reviewed here investigated changes in liver fat content, visceral adipose tissue and abdominal subcutaneous adipose tissue with tirzepatide compared to insulin degludec in a subpopulation of SURPASS-3 participants. These 296 individuals met the inclusion criteria for SURPASS-3 but also had an elevated fatty liver index, indicating the presence of significant non-alcoholic fatty liver disease (NAFLD). They underwent an MRI liver scan at baseline and again after 52 weeks of either tirzepatide (5, 10 or 15 mg) or titrated insulin degludec.

Mean baseline liver fat content was 15.71%. In pooled analysis, tirzepatide 10 mg and 15 mg were found to reduce liver fat content by more than half (–8.09%), compared with a reduction of 3.38% with insulin degludec. Significant reductions in visceral adipose tissue and abdominal subcutaneous adipose tissue were also observed. Alongside these benefits, there were significant improvements in glycaemic control, lipid profiles, total body weight and liver enzymes (ALT and AST). Unfortunately, no assessment of liver fibrosis, either by biopsy or non-invasive methods such as elastography, was undertaken.

These results position tirzepatide as a promising future treatment for NAFLD, which is now one of the fastest-growing indications for liver transplantation in the Western world. NAFLD is closely associated with type 2 diabetes and is an independent predictor of all-cause mortality. The condition is an impending public health crisis, and effective interventions for it are urgently required to prevent a major cause of chronic liver disease worldwide. ■

Ludvik B, Giorgino F, Jódar E et al (2021) Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* **398**: 583–98


Articles

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

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