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Tirzepatide reduces weight and insulin dose and improves body composition in type 1 diabetes: a 12-week, randomised, double-blind, placebo-controlled trial (TIRTLE1)

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Background and aims: Overweight and obesity are prevalent in type 1 diabetes (T1D) and contribute to cardiovascular risk. Tirzepatide (TZP) is a dual gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, developed for use in type 2 diabetes and for obesity. TZP has not been previously studied in T1D in a controlled setting.

Materials and methods: Adults with T1D (duration > 2 years, age 18-60 years, BMI > 30kg/m^2) were randomised 1:1 to receive weekly subcutaneous TZP (2.5mg for 4 weeks, 5.0mg thereafter or maximum tolerated dose) or placebo for 12 weeks. The primary endpoint was change in body weight over the trial period. Secondary outcomes included change in insulin dose, HbA1c, diet features and body composition.

Results: Of 24 adults with T1D (mean±SD; 41±10 years, BMI 33.7±3.2 kg/m^2, HbA1c 7.3±1.2%, total daily dose of insulin median 69.1 units/day [interquartile range 41.9 to 86.7 units/day], 42% female, 13 insulin pump, 11 multiple daily injection), 22 participants completed the study. After 12 weeks, TZP was associated with significant reductions in body weight vs placebo (mean difference -8.7 kg [8.8% reduction], 95% confidence interval [CI] -12.0 to -5.5 kg; p<0.0001). Of the weight lost, 82% was fat mass (mean difference -7.2 kg [95% CI -10.5 to -3.9 kg] vs placebo; p=0.0002). In contrast, the mean difference in fat-free mass was -1.8 kg [95% CI -3.75 to +0.1 kg] vs placebo; p=0.06). TZP was associated with reductions in HbA1c (mean difference -0.35% [95% CI -0.7 to 0.0%] vs placebo; p=0.05) and total daily insulin dose (geometric mean -24.2 units/day TZP and -0.3 units/day placebo [insulin dose -35.1% from baseline vs placebo, 95% CI -46.5 to -21.3%; p=0.0002). Amongst pump users, insulin dose reductions were observed early (-22% from baseline insulin dose at 2 weeks vs placebo; p=0.07, and -42% from baseline at 6 weeks vs placebo; p=0.007). Overall energy intake was reduced (mean difference -429 kcal/d [95% CI -852 to -5 kcal/d] vs placebo; p=0.05) and self-reported physical activity level (International Physical Activity Questionnaire Short Form) did not change. Two study participants dropped out (TZP n=1 due to increased anxiety coinciding with difficulties attending study visits, placebo n=1 due to loss of interest in the study). There were no episodes of DKA or severe hypoglycaemia in either group.

Conclusion: In the first randomised trial of TZP in T1D, TZP was associated with favourable changes in weight and in body composition (i.e. loss of fat mass with relative preservation of fat-free mass) and marked insulin dose reductions. Future studies are required to assess efficacy and safety in a phase 3 setting and to understand the mechanisms of the rapid TZP-driven metabolic impacts specific to T1D.

Clinical Trial Registration Number: ACTRN12624000111572

Supported by: St Vincent's Clinic Foundation, Australian Diabetes Society, JDRF Australia Grant# 3-SRA-2023-1296-M-N

Disclosure: **J.R. Snaith:** Grants; St Vincent's Clinic Foundation, Australian Diabetes Society Type 1 Diabetes Rising Star Award, JDRF Australia Rebecca Davies Fellowship (Grant# 3-SRA-2023-1296-M-N), the recipient of the Commonwealth of Australia grant for Accelerated Research under the Medical Research Future Fund.