**Title**: Tirzepatide reduces liver steatosis in a murine model of insulin-deficient diabetes and obesity

**Background**: Obesity in people with type 1 diabetes (T1D) induces insulin resistance which, together with inherent insulin deficiency, makes glycaemic management more difficult. Furthermore, obesity increases cardiometabolic complications of T1D such as metabolic-associated fatty liver disease (MAFLD), compared to T1D alone. Weight loss is the most effective treatment for MAFLD, traditionally relying upon lifestyle intervention. Incretin-based therapies (IBTs) has emerged as an effective means to improve advanced liver disease in the setting of obesity, yet their benefits in MAFLD-associated T1D and obesity has not been established.

**Aim**: To explore the effect of tirzepatide (TZP) on liver outcomes in a mouse model of concurrent insulin-deficient diabetes and obesity.

**Method**: 8-week-old C57Bl/6J mice were randomly assigned to 4 treatment groups: Chow, Chow + STZ (DM), high-fat diet (HFD) + STZ (DMO), and DMO + TZP (DMO-TZP). STZ was given as 5 consecutive daily doses (55mg/kg/day), rendering the mice insulin deficient. TZP was administered thrice weekly (40nmol/kg s.c.) for 24 weeks. Histological scores, immunohistochemistry and RT-PCR of liver tissue was observed.

**Results**: The DMO group had histological scores indicative of MAFLD, with increased steatosis and ballooning.TZP significantly reduced steatosis and ballooning (DMO vs DMO-TZP, both P<0.005). TZP improved lipid metabolism, e.g., confirmed by restored fatty acid synthase (FAS) protein and gene expression (DMO vs DMO-TZP, P<0.01 and P<0.05, respectively). There were modest changes in hepatic inflammation and oxidative stress measures.

**Conclusion**: Evidence of MAFLD was observed in this murine model of T1D and obesity, that was significantly reduced by TZP, suggesting a protective role of TZP in MAFLD. Given that the cardiometabolic complications of T1D are exacerbated by obesity, TZP may be a useful early treatment to reduce MAFLD and its progression. Further studies utilizing models that develop more severe liver pathology are warranted to fully elucidate the therapeutic potential of TZP in mitigating progression to advanced liver disease.