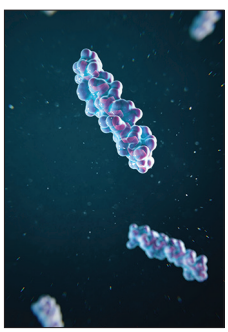
Dual incretin agonist for paediatric type 2 diabetes: an eagerly awaited opportunity



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Although type 2 diabetes is often regarded as a disease of ageing, cases of type 2 diabetes in children and adolescents have climbed sharply since the turn of the century. The US prevalence of type 2 diabetes in youth aged 10–19 years increased significantly from 0·34 (95% CI 0·31–0·37) per 1000 in 2001 to 0·67 (0·63–0·70) per 1000 in 2017, revealing a 95·3% (95% CI 77·0–115·4) relative increment in a mere 16 years, with the largest absolute increases seen in non-Hispanic Black and Hispanic youth.[1] Epidemiological models project that if the occurrence of type 2 diabetes continues at the current rate, the prevalence of youth-onset type 2 diabetes among US youth will increase by more than 700% by 2060 compared with prevalence in 2017.[2] Global data also reveal an astonishing increase in type 2 diabetes in adolescents and young adults, with incidence rising from 56·0 per 100 000 population in 1990 to more than double at 123·9 per 100 000 in 2021.[3] Furthermore, in the not-too-distant past, new cases of diabetes in youth were almost exclusively type 1 diabetes in the USA, but in 2017–18, the annual incidence of new cases of type 2 diabetes in children and adolescents aged 10 to <20 years was 17·9 per 100 000, nearly mirroring the type 1 diabetes annual incidence of 22·2 per 100 000 children and adolescents younger than 20 years.[4] Given the ongoing global epidemic of childhood overweight and obesity,[5] it will likely become harder to distinguish clearly between type 1 and type 2 diabetes in youth.

Risk factors for youth-onset type 2 diabetes include obesity, unhealthy diets, inadequate physical activity along with increased sedentary behaviours (eg, screen time), and family history of diabetes, with these obesogenic environmental factors tending to cluster according to socioeconomic status in the USA and around the globe, all of which add to the complexity of preventing and treating type 2 diabetes in youth.[6] Therefore, we welcome the randomised, placebo-controlled clinical trial by Tamara S Hannon and colleagues in *The Lancet* that describes the efficacy and safety of tirzepatide, a dual incretin agonist, in children and adolescents (aged 10 to <18 years) with type 2 diabetes.[7]

Hannon and colleagues' study included 39 sites in Australia, Brazil, India, Israel, Italy, Mexico, the UK, and the USA. Following screening of 146 young people, 99 eligible children and adolescents were randomly assigned (1:1:1) to 5 mg tirzepatide, 10 mg tirzepatide, or placebo given by subcutaneous injection once weekly. The participants' mean age was 14·7 years (SD 1·8), their mean baseline glycated haemoglobin (HbA_{1c}) was 8·04% (1·23), and 60 (61%) were female and 39 (39%) male. The primary efficacy outcome was change in HbA_{1c} assessed at 30 weeks, with safety outcomes assessed at 30 weeks and 52 weeks, which included a 22-week open-label extension period in which the tirzepatide groups continued their current doses and the placebo group received 5 mg tirzepatide weekly.

Hannon and colleagues report that HbA_{1c} was significantly lower in the pooled tirzepatide group versus the placebo group at 30 weeks by around 2·3%, a remarkable clinically meaningful difference (mean reduction of 2·23% in the pooled tirzepatide group *vs* an increase of 0·05% in the placebo group [estimated treatment difference −2·28%, 95% CI −2·87 to −1·69; p<0·0001]). Furthermore, other secondary outcomes at 30 weeks with respect to fasting glucose levels, BMI, and BMI standard deviation score significantly favoured the pooled tirzepatide group as well as the individual tirzepatide treatment groups versus the placebo group. Glycaemic and weight loss benefits were sustained at 52 weeks. In addition, the tirzepatide groups demonstrated improvements in cardiovascular risk factors, including blood pressure, lipid levels, and waist circumference, versus the placebo group. The most common adverse events were gastrointestinal, as expected; only two participants in the tirzepatide groups discontinued treatment due to adverse events, and adverse events in general were similar to those reported in adult trials. Overall, this clinical trial demonstrated substantial clinical benefit of tirzepatide in children and adolescents with type 2 diabetes followed up for 1 year.

The trial is, however, limited by the need to evaluate: treatment durability with longer follow-up; the use of tirzepatide with other agents such as SGLT2 inhibitors; and opportunities to reduce or possibly discontinue the medication once the weight loss goal is achieved, especially given the young age of these individuals

possibly facing decades of treatment that will include the reproductive years (GLP-1 receptors are not recommended for use in pregnancy[8]).

Traditionally, therapeutic options for type 2 diabetes in youth have been limited and less effective than in adults with type 2 diabetes. Until recently, metformin and insulin were the only approved medications for paediatric type 2 diabetes. Yet, the TODAY study of youth-onset type 2 diabetes demonstrated high rates of glycaemic failure, with nearly half (46%) of the study sample unable to maintain glycaemic control at a median time of 11·5 months.[9] The treatment group receiving both metformin and rosiglitazone had a 25% reduction in treatment failure compared with metformin treatment alone. This aggressive loss of glycaemic control was coupled with an accelerated onset of complications, with 60% developing at least one microvascular complication, and 28% developing two or more at a mean age of 26 years and mean duration of type 2 diabetes of only 13 years.[10]

The TODAY study findings heralded the need for early combination therapy for youth-onset type 2 diabetes to preserve glycaemic control, now made possible given the tirzepatide trial and other clinical trials followed by regulatory approvals of type 2 diabetes medications previously approved only for use in adults. There are now three GLP-1 receptor agonists and three SGLT2 inhibitors approved by both the European Medicines Agency and the US Food and Drug Administration for use in paediatric patients with type 2 diabetes aged 10 years and older. Many of these studies took years to complete until innovative approaches to clinical trial design were adopted. For example, trials have used a single control group against multiple medications and have combined different doses of a medication (eg, SGLT2 inhibitors and DPP-4 inhibitors) into a single group for outcomes analysis, as in the current clinical trial.[7,11] These trials have included investigations of GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and tirzepatide. Yet, as shown in a recent systematic review and meta-analysis of pharmacological treatments for type 2 diabetes in children and adolescents, there were only 12 clinical studies in youth that included a mere 1658 participants.[12] Another recent systematic review and meta-analysis of GLP-1 receptor agonists in overweight or obese adolescents identified only seven clinical trials including 576 youth participants.[13] By contrast, the single placebo-controlled clinical trial of tirzepatide versus placebo in adults with type 2 diabetes included 938 participants.[14] This highlights the ongoing need for larger, more inclusive clinical trials in paediatric populations to ensure that recent therapeutic advances in type 2 diabetes are equitably extended to children and adolescents.

Given the mounting global prevalence of type 2 diabetes in youth and adverse impacts with respect to loss of durable glycaemic control, related to more rapid decline in β-cell function in youth-onset type 2 diabetes than in adults, coupled with the premature onset of diabetes complications, the significant and clinically meaningful improvements in glycaemic control and weight loss with tirzepatide are welcome. However, there remains a need for large, long-term studies of incretin therapies in youth-onset type 2 diabetes to better understand their impact on complications, their long-term safety when initiated in childhood, and their management during the reproductive years, as well as a societal reassessment of factors leading to the global obesity and diabetes epidemics along with mitigation strategies.[15]

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*Elvira Isganaitis, *Lori M Laffel*
lori.laffel@joslin.harvard.edu

Research Division, Joslin Diabetes Center, Boston, MA 02215, USA (EI, LML); Department of Pediatrics, Harvard Medical School, Boston, MA, USA (EI, LML)

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