Commentary on "Effects of once-weekly dulaglutide on juvenile type 2 diabetes mellitus and obesity in Korea: a pilot study"

Han Hyuk Lim
Department of Pediatrics, Chungnam National University College of Medicine, Daejeon, Korea

The prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents has been gradually increased, correlating with the steadily rising obesity rate among them in Western countries as well as in Korea.1,2 The key pathophysiology of T2DM is insulin resistance with relative insulin deficiency, hyperglucagonemia in pancreatic alpha cells, and impaired incretin action.3,4 Because this deterioration of beta-cell function in juvenile T2DM is more aggressive than in adult T2DM, glycemic worsening was more frequent in in children and adolescents than in adults, and the long-term cardiovascular or renal complications in juvenile T2DM are more rapid and severe than in age-matched patients with T1DM or adults with T2DM.5,6 It is critical for juvenile T2DM to initiate effective treatment that can restore their beta-cell function.

Despite many new drugs for the treatment of adult T2DM, medication for juvenile T2DM has been limited to metformin in most countries and sulfonylurea in some, and there are only five agents approved by the U.S. Food and Drug Administration for children and adolescents with T2DM.5,6 In the guidelines of the International Society for Pediatric and Adolescent Diabetes, American Diabetes Association, and European Association for the Study of Diabetes, the initial therapy for youth-onset T2DM is oral metformin with healthy lifestyle changes. In the presence of hemoglobin A1c (HbA1c) ≥9.5% or ketosis/ketonuria/ketoacidosis, intermediate- or long-acting injectable insulin (0.25–0.5 units/kg) is required as second-line therapy.5,8 However, the TODAY (treatment options for type 2 diabetes in adolescents and youth) trial showed that metformin effectively controlled glycemia in only half of youth-onset T2DM, and neither metformin nor insulin was able to reduce the progressive decline in beta-cell function.9

As of 2019, liraglutide, exenatide, and dapagliflozin have been approved for use in juvenile T2DM. Liraglutide and exenatide, injectable glucagon-like peptide-1 inhibitor agonists (GLP-1RAs), have been approved for use in patients with T2DM aged 10 years and older.3,5 GLP-1RAs act through glucose-dependent insulin release, suppression of glucagon secretion during hyper- or euglycemia, slowing of gastric emptying, and reduction in body weight.10 Injection of a GLP-1RA with oral metformin±basal insulin in juvenile T2DM showed an effective reduction in HbA1c compared with placebo, with gastrointestinal side effects similar to those seen in adult studies.5,10 Dapagliflozin, a sodium-glucose transporter-2 (SGLT2) inhibitor, has also been approved for use in children over 10 years of age. In adults with T2DM, dapagliflozin has shown benefit in lowering their HbA1c and reducing adverse cardiovascular and microvascular complications. The efficacy and safety of an SGLT2 inhibitor with oral metformin±basal insulin in juvenile T2DM was similar to that in adult studies and was superior to that of the control group.11 In addition, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors has shown limited success or adverse concerns in juvenile T2DM.5

In 2014, once-weekly dulaglutide, a GLP-1RA, was approved for adult T2DM. And a phase 3 trial of once-weekly injectable dulaglutide for the treatment of juvenile T2DM aged 10–18 years was reported in 2022.11 In this trial, dulaglutide showed a more effective reduction in HbA1c than placebo in juvenile T2DM treated with lifestyle modification ± metformin or
insulin, with no serious adverse events.\textsuperscript{10)}

The current study is the first report to determine the effects and side effects of once-weekly dulaglutide in juvenile T2DM under the age of 18 years in Korea.\textsuperscript{11)} Despite the small number, this study also indicated that the use of dulaglutide may be another potential therapeutic, safe option in young patients with poorly controlled T2DM. However, there are still some concerns about the relationship between the use of GLP-1RAs and growth, development or cancer in children and adolescents. Nationwide, multicenter, larger group studies are needed in young people with T2DM to determine the future treatment strategies including dulaglutide.

**Conflicts of interest:** No potential conflicts of interest relevant to this article were reported.

**References**