Elevation of Fasting GLP-1 Levels in Child and Adolescent Obesity: Friend or Foe?

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Abbreviations: DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin-6; T2D, type 2 diabetes.

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Abstract

Glucagon-like peptide-1 (GLP-1) receptor agonists have been gaining much attention as a therapeutic approach to type 2 diabetes and obesity. Stinson et al recently reported that fasting GLP-1 is higher in children and adolescents with overweight/obesity and that it associates with cardiometabolic risk factors in a cross-sectional study comprising more than 4000 subjects. Obvious questions include why fasting GLP-1 is significantly increased in children and adolescents with overweight/obesity and why this is correlated with cardiometabolic risks. It has been shown that the inflammatory cytokine interleukin-6 (IL-6) stimulates GLP-1 secretion from pancreatic α-cells. IL-6-induced GLP-1 secretion could therefore play a role in expanding the β-cell reservoir in compensation for increased insulin needs due to exacerbation of insulin resistance. On the other hand, augmented GLP-1 secretion leads to increased insulin secretion, thereby enhancing hepatic lipogenesis and stimulating adipogenesis, which might underlie the associations of fasting GLP-1 with % body fat, triglycerides, and alanine aminotransferase. It is also possible that GLP-1 levels are naturally increased to oppose body weight gain to maintain body weight. However, it is important to note the differing biological effects of GLP-1 at physiological and pharmacological levels, which are evident in body weight reduction by GLP-1 receptor agonists and DPP-4 inhibitors. The Stinson study clearly demonstrated that fasting GLP-1 associates with overweight/obesity and cardiometabolic risk factors in children and adolescents. However, additional experiments need to be carried out to fully understand the relevance of these observations to human disease and health.
Glucagon-like peptide-1 (GLP-1) receptor agonists have been gaining much attention as a therapeutic approach to type 2 diabetes (T2D) and obesity (1, 2). Previous clinical studies, conducted mainly in adults, demonstrated that GLP-1 receptor agonists ameliorate the secretions of insulin and glucagon in a glucose-dependent manner and delay gastric emptying, thereby improving postprandial glucose excursion (1, 2). GLP-1 receptor agonists also suppress appetite and reduce body weight (1, 2). Furthermore, GLP-1 agonists ameliorate dyslipidemia and hypertension as well as exerting anti-inflammatory effects and improving endothelial function, thereby suppressing adverse cardiovascular events in adults with T2D (1, 2).

Inspired by the pleiotropic effects of GLP-1 receptor agonists (1, 2), fasting and postprandial levels of GLP-1 have been investigated in studies of adults and children with diabetes, obesity, and cardiometabolic risk factors. Previously, some cross-sectional studies reported that fasting GLP-1 levels are higher in adults with T2D and obesity, while others found no difference. A recent longitudinal study reported a significant increase of fasting GLP-1 levels among female adults with obesity who were losing body weight by a healthy diet based on the Nordic Nutrition Recommendations, while no significant change was observed among those losing body weight by the “Paleolithic Diet” (3). The conflicting results may be in part due to the relatively small sample size of the studies. Small sample size is also a cause for concern regarding previous cross-sectional and longitudinal studies evaluating fasting GLP-1 levels in children and adolescents with obesity. Well-designed cross-sectional studies and randomized controlled trials with an adequate sample size are therefore needed. Recently, Stinson et al reported that fasting GLP-1 levels are higher in children and adolescents with overweight/obesity compared with the general population in a cross-sectional study comprising more than 4000 subjects (4). Stinson et al also demonstrated that a 1-SD increase in fasting GLP-1 levels is associated with higher body mass index, insulin resistance, dyslipidemia, and increased alanine aminotransferase, hyperglycemia, and hypertension (4), indicating that fasting GLP-1 levels can serve as an indicator of cardiometabolic risk.

Obvious questions include why fasting GLP-1 levels are significantly increased in children and adolescents with overweight/obesity and why this is correlated with cardiometabolic risks. It is recognized that GLP-1 is secreted from pancreatic α-cells as well as from intestinal L-cells and that the inflammatory cytokine interleukin-6 (IL-6) stimulates GLP-1 secretion from pancreatic α-cells (5). As serum IL-6 levels are increased in individuals with obesity, IL-6-induced GLP-1 secretion could play a role in enhancing β-cell proliferation to expand the β-cell reservoir in compensation for increased insulin needs due to visceral fat accumulation and subsequent exacerbation of insulin resistance (5). While some studies failed to replicate IL-6-induced GLP-1 secretion, this scenario reasonably explains the positive association of fasting GLP-1 levels with homeostatic model assessment of insulin resistance (HOMA-IR) (odds ratio 1.59). Therefore, it is important to clarify the association of IL-6 with fasting GLP-1 levels in large biobanks such as that used by Stinson et al (4). On the other hand, augmented GLP-1 secretion leads to increased insulin secretion, thereby enhancing hepatic lipogenesis and stimulating adipogenesis, which could underlie the associations of fasting GLP-1 levels not only with HOMA-IR, insulin, and C-peptide but also with % body fat and levels of triglycerides and alanine aminotransferase (4). In this scenario, a raised fasting GLP-1 level might initiate a vicious cycle that increases cardiovascular risks in obese children and adolescents. It is therefore important to determine whether fasting GLP-1 levels are decreased by body weight loss by healthy diet and exercise with and without pharmacological/surgical interventions in randomized controlled trials with adequate sample size.

Of course, it is possible that GLP-1 levels are naturally increased to oppose body weight gain or to maintain body weight, as it has recently been shown that overfeeding results in increased fasting levels of GLP-1 (6). GLP-1 receptors are expressed in the central nervous system and their activation by intracranial GLP-1 administration suppresses appetite (1, 2). It has been shown that the GLP-1 receptor agonists liraglutide and semaglutide reach the central nervous system and activate neurons involved in appetite control, but no difference was observed in energy intake or body weight gain between wild-type and GLP-1 receptor-deficient mice (1, 2). While some studies have reported increased biologically intact GLP-1 levels within the physiological range together with reduced body weight in rodents treated by dipeptidyl-peptidase (DPP)-4 inhibitors, DPP-4 inhibition was found to have little effect on appetite or body weight in human (1, 2). Thus, it is important to note the differing biological effects of GLP-1 at physiological and pharmacological levels, which are evident not only in body weight reduction but also in the results of cardiovascular outcome trials for GLP-1 receptor agonists and DPP-4 inhibitors (1). Of course, the effects
of GLP-1 receptor agonists and DPP-4 inhibitors on cardiovascular disease, diabetes, and other chronic diseases may be influenced by the degree of adiposity and dietary habits (1).

Differences in the biological effects at physiological and pharmacological levels are also critical for glucose-dependent insulinotropic polypeptide (GIP) levels. GIP and GLP-1 are the incretins, which enhance insulin secretion in a glucose-dependent manner and ameliorate postprandial glucose excursion (2). Recent development of GIP receptor/GLP-1 receptor co-agonists has shown the importance of GIP at pharmacological levels, which suppresses appetite and reduces body weight substantially (1, 7), while GIP at physiological levels facilitates fat accumulation and body weight gain (2). Accumulating evidence in rodent and human support this relationship between GIP and obesity. GIP antagonism has been gaining attention recently as a therapeutic approach to obesity and nonalcoholic fatty liver disease (8). Thus, measuring fasting GIP levels in a cohort similar to that used by Stinson et al (4) would be helpful in clarifying the associations of fasting GIP levels with cardiometabolic risk factors.

The Stinson study has clearly demonstrated that fasting GLP-1 levels associate with overweight/obesity and cardiometabolic risk factors in children and adolescents (4). However, additional experiments need to be carried out to fully understand the relevance of these observations to human disease and health. While it has been more than 100 years since the discovery of the incretin concept by Moore and colleagues (2), the journey to understand the incretin system and its role in obesity and metabolic disorders continues.

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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