Incretin Hormones: Pathophysiological Risk Factors and Potential Targets for Type 2 Diabetes

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Type 2 diabetes (T2D) is a multifaceted metabolic disorder associated with distinctive pathophysiological disturbances. One of the pathophysiological risk factors observed in T2D is a dysregulation of the incretin hormones glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1). Both hormones stimulate insulin secretion by acting postprandially on pancreatic β-cell receptors. Oral glucose administration stimulates increased insulin secretion in comparison with isoglycemic intravenous glucose administration, a phenomenon known as the incretin effect. While the evidence for incretin defects in individuals with T2D is growing, the etiology behind this attenuated incretin effect in T2D is not clearly understood. Given their central role in T2D pathophysiology, incretins are a promising target for T2D therapeutics. The present review synthesizes the recent attempts to explain the biological importance of incretin hormones and explore potential pharmacological approaches that target the incretins.

**Key words:** Glucagon-like peptide-1, Glucose-dependent insulinotropic polypeptide, Type 2 diabetes, incretin; Oral glucose tolerance test; Insulin; Glucose
INTRODUCTION

An estimated 463 million cases of diabetes were reported globally in 2019. It has been estimated that 90% of the cases are type 2 diabetes (T2D).\textsuperscript{1,2} Once thought to be exclusively seen in adults, youth-onset T2D has emerged as an prevalent condition in parallel with pediatric obesity epidemic.\textsuperscript{3} From 2002 to 2012, an annual increase of 7.1% in cases per 100,000 youths between 10 and 19 years of age was reported in the United States.\textsuperscript{4} The key pathophysiological feature of T2D is pancreatic β-cell dysfunction against a backdrop of insulin resistance in muscle, liver, and adipose tissues.\textsuperscript{5-10} Recent clinical observations have revealed that obese youths with impaired glucose tolerance (IGT) and/or recently diagnosed T2D have exacerbated pathophysiological dysregulations, including severe (approximately 2-fold) impairments in hepatic and/or peripheral insulin sensitivity, compared with equally obese adult counterparts, despite similar disease progression in both age groups.\textsuperscript{11-13} Metformin, a commonly prescribed monotherapy, is used by up to 88% of individuals with T2D,\textsuperscript{14,15} and prior to 2019 was the only non-insulin antidiabetic agent approved for youths.\textsuperscript{16,17} Metformin, despite being an exclusively approved monotherapy available for children, has not been effective in restoring β-cell function and glycemic control (persistent maintenance of glycosylated hemoglobin [HbA1c] <8%) in youths with T2D.\textsuperscript{18} As a result, interest in utilizing incretin-based therapies for treating T2D has been growing. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), incretin-based therapeutics, were first approved by the U.S. Food and Drug Administration in 2005 to treat T2D in adults, and in 2019 for youths.\textsuperscript{17,19}

Given the important role of incretins in the development and the treatment of T2D, this narrative review focuses on (1) the biological background of incretins; (2) the pathophysiological deterioration of incretin effects and/or incretin hormones in adults and youth; and (3) the recent use of incretin therapy in T2D. We also discuss future directions that must be addressed to acquire a thorough understanding of the potential of incretin hormones as therapeutic agents for T2D.
HISTORY OF INCRETTINS

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, first described in 1973 and 1987, respectively,20-23 are the two known incretin hormones.24,25 The development of radioimmunoassays allowed researchers to quantitatively explore their mechanisms.26 Prior to this invention in 1932, LaBarre et al.27 established the incretin concept: a humoral factor released from the intestines to lower blood glucose after a meal. Through in vitro processing of duodenal extracts, LaBarre et al.27 found crude secretion of the incretins acted on the pancreas to stimulate insulin. Efforts to understand incretin hormones have continued since then. Common criteria for incretin classification include: (1) be a gastrointestinal factor, (2) be released in response to nutrients, and (3) stimulate insulin secretion in a glucose-dependent manner at physiological levels.28 GIP and GLP-1 are the only known hormones that fit these criteria.25

BIOLOGY OF INCRETTINS

GLP-1 is a 30-amino-acid peptide hormone synthesized in and secreted from enteroendocrine L cells,29 which are found in the small and large intestine.24 In the small intestine, the density of L cells is greater in the distal ileum region compared with the proximal jejunum.30 GLP-1 exists in several different forms: GLP-1 (1-37), or 1-36amide; and 2 truncated forms, GLP-1 (7-36) or amidated GLP-1, and GLP-1 (7-37), or extended GLP-1.30,31 GLP-1 (7-36) and GLP-1 (7-37) have a comparable potential to stimulate the secretion of insulin and C-peptide;32 however, GLP-1 (1-37) has a considerably lower insulinotropic effect.33 In humans, the majority of circulating GLP-1 is in 1 of the 2 truncated forms; approximately 80% from GLP-1 (7-36), and 20% from GLP-1 (7-37).34 GLP-1 secretion is stimulated by nutrient intake, specifically carbohydrates and fats, while proteins appear to be less effective.35 In general, GLP-1 can be detected at low concentrations during fasting.36 During a postprandial state, a 2- to 3-fold increase in GLP-
1 concentrations can be observed within minutes.\textsuperscript{36,37} Postprandial time to peak GLP-1 concentration depends on the contents of the meal. Oral glucose administration during an oral glucose tolerance test (OGTT) can cause a peak at approximately 20 minutes, while a standard mixed meal takes closer to 60 to 90 minutes.\textsuperscript{38,39} Once in circulation, GLP-1 travels and binds to the GLP-1 receptor (GLP-1R) on pancreatic \(\beta\)-cells, where it augments insulin secretion and lowers blood glucose.\textsuperscript{24} GLP-1 is a strong inhibitor of glucagon secretion; however, this effect depends on glucose concentration and does not pose a risk of hypoglycemia.\textsuperscript{40} Only 10\% to 15\% of endogenously released GLP-1 reaches systemic circulation,\textsuperscript{30} potentially because of dipeptidyl peptidase 4 (DPP-4), which cleaves active GLP-1 (7-36 amide) and GLP-1 (7-37) at the N-terminal dipeptide, generating inactive GLP-1 (9-36 amide) or GLP-1 (9-37). These shortened GLP-1 molecules have low-affinity ligands for GLP-1R.\textsuperscript{41} This observation has given rise to a class of drugs known as DPP-4 inhibitors, which increase active GLP-1 and insulin secretion.\textsuperscript{42} The half-life of GLP-1 has been estimated at approximately 1 to 3 minutes.\textsuperscript{43}

GIP is a 42-amino-acid peptide hormone synthesized and secreted from enteroendocrine K cells.\textsuperscript{24} Unlike L cells, K cells are found primarily in proximal regions of the small intestine, such as the duodenum and proximal jejunum.\textsuperscript{24,25} While GIP is also secreted in response to a meal,\textsuperscript{25} fat was found to be a more potent GIP secretagogue than glucose, even when matched for calories.\textsuperscript{44} Once in systemic circulation, GIP causes insulinotropic effects by binding to the gastric inhibitory polypeptide receptor (GIPR) on \(\beta\)-cells.\textsuperscript{24} Unlike GLP-1’s inhibition of glucagon, GIP has been shown to increase glucagon secretion.\textsuperscript{45} GIPRs are also located on \(\alpha\)-cells.\textsuperscript{46} As with GLP-1, GIP can be found in small concentrations during fasting. However, unlike the 2- to 3-fold increase in GLP-1 typically observed after a meal, GIP concentrations may increase by a factor of 10.\textsuperscript{47} DPP-4 will degrade GIP by cleaving the first 2 amino acids (Tyr and Ala) at the N terminus. This turns active GIP (1-42) into inactive GIP (3-42) with little to no insulinotropic effect.\textsuperscript{48} After a meal, approximately 55\% of the total GIP is in the active form, with the kidneys constituting the major site of elimination.\textsuperscript{49} Consequently, the half-life of active GIP is 5 to 7 minutes.\textsuperscript{48}
THE INCRETIN EFFECT

The insulin response is enhanced when glucose is consumed orally compared with intravenous (IV) administration at the same concentration. This phenomenon is known as the incretin effect. Patients with T2D reportedly experience a decreased incretin effect compared with those with normal glucose tolerance (NGT). During an OGTT, incretin contributes 73% if the total insulin response in healthy adults, but only 36% in adults with T2D. The following findings are drawn from a selective review of studies that quantified the incretin effect in subjects with T2D and/or IGT compared with those with NGT.

Nauck et al. evaluated the incretin effect in 14 adults with T2D and eight age- and weight-matched NGT counterparts. Participants underwent a 3-hour OGTT and isoglycemic IV glucose administration on separate days. As measured by the insulin response to oral glucose compared with IV glucose, the incretin effect was reduced by approximately 50% in subjects with T2D vs. those with NGT (36.0±8.8% vs. 72.8±6.9%; P<0.05). This was the first study to describe an impaired incretin effect in T2D vs. NGT subjects. Muscelli et al. investigated the independent effects of obesity and glycemia on the incretin effect in 51 adults (24 NGT, 17 IGT, and 10 T2D) who completed a 3-hour OGTT and an intravenous glucose tolerance test (IVGTT). The incretin effect was defined as the oral-to-IV ratio of insulin secretion or oral-to-IV β-cell glucose sensitivity (βCGS). Both were significantly reduced in T2D subjects compared with NGT subjects. Further analysis of the subjects put them into one of three categories of body mass index (BMI; 25, 30, and 45 kg/m²) regardless of glycemic status, with similar HbA1c levels in the three BMI groups. The incretin effect decreased with BMI, according to observations of both models of the incretin effect (oral-to-IV ratio: BMI kg/m² 25, 1.8±0.6 vs. BMI 30 kg/m², 1.4±0.3 vs. BMI 35 kg/m², 1.1±0.2%, P=0.0002; βCGS: 2.1±1.0 vs. 1.6±0.8 vs. 1.3±0.5, P=0.02). These results suggest that obesity and dysglycemia can impair the incretin effect, independent of each other. Another study by Muscelli et al. explored the impact of the incretin effect and secretion on β-cell function in 10 IGT and 11 NGT adults during a 3-hour OGTT and IVGTT. The incretin effect was estimated by using either C-peptide or the
insulin response of oral-to-IV glucose. While the findings were not statistically meaningful, a clear decrease in adults with IGT vs. those with NGT was evident. This suggests that incretin defects can be accelerated from prediabetes to T2D, despite an initial impairment of incretins potentially occurring in adults with IGT. Knop et al.\textsuperscript{55} examined differences in incretin response in adults during OGTT and isoglycemic IV glucose administration on different days. The study included four groups: (1) patients with chronic pancreatitis (CP) and secondary diabetes; (2) patients with CP and NGT; (3) patients with T2D; and (4) healthy controls. Each group had eight participants. The incretin effect, which was calculated by relating the difference in integrated β-cell secretory responses between stimulation with oral and isoglycemic IV glucose, decreased in individuals with T2D vs. their healthy counterparts (44\(\pm\)9\% vs. 73\(\pm\)6\%, \(P<0.05\)). These findings agree with the aforementioned studies showing a reduced incretin effect in T2D vs. NGT subjects. Another study by Knop et al.\textsuperscript{56} explored the impact of obesity on incretin secretion. Four adult groups with eight participants each underwent 4-hour OGTT and isoglycemic IV glucose infusion: (1) obese with T2D, (2) obese with NGT, (3) lean with T2D, and (4) lean with NGT. The incretin effect, which was calculated by relating the difference in integrated β-cell secretory responses between stimulation with OGTT and IV glucose, was reduced in lean subjects with T2D vs. lean subjects with NGT (29\(\pm\)8\% vs. 53\(\pm\)4\%, \(P<0.05\)). A tendency toward a significantly reduced incretin effect was reported in obese participants with T2D vs. lean participants with T2D (7\%\(\pm\)7\% vs. 29\%\(\pm\)8\%, \(P=0.06\)). The study demonstrated that glycemic and obesity status may play independent roles in reducing the incretin effect, a finding that agrees with that of Muscelli et al.\textsuperscript{54} Taken together, these studies suggest that the incretin effect is progressively exaggerated as glycemic and obesity status worsens in adults.

To date, few studies on the incretin effect in pediatric population have been published, and just three describe the incretin effect in youth-onset T2D compared with their NGT counterparts. Michaliszyn et al.\textsuperscript{50} examined the relationship between the incretin effect and β-cell function in 255 obese youths (a mixture of African-American and Caucasian adolescents) across the spectrum of glucose tolerance from 173 NGT to 48 IGT to 34 T2D. Participants underwent an OGTT and a hyperglycemic clamp (225 mg/dL)
in random order, and the incretin effect was calculated as the ratio of OGTT-βCGS to the 2-hour hyperglycemic clamp-βCGS. The study found that the incretin effect was significantly reduced by 32% and 38% in youths with IGT and T2D, respectively, when compared with their NGT counterparts, indicating a progressive decline in the incretin effect across glucose tolerance levels. An impaired incretin effect in youths with T2D is in line with other adolescent and adult findings. In another study by Yeow et al., the incretin effect and GLP-1 response were examined in 25 overweight Asian youths with T2D and 15 overweight Asian youths without T2D. The incretin effect, which was estimated from the C-peptide response between stimulation of oral and IV glucose, was reduced by approximately 80% in youths with T2D compared with those with NGT (12.1%±8.93% vs. 70.0%±4.03%). To our knowledge, this is the largest reduction observed in the incretin effect in those with T2D vs. NGT. Last, Aulinger et al. examined the effect of obesity on the incretin effect in three groups: (1) 10 obese subjects with T2D, (2) 10 obese subjects with NGT, and (3) 8 lean subjects with NGT. Members of the group with T2D had good glycemic control (mean HbA1c, 5.9%±0.2%) at the time of the study. The incretin effect, as calculated by the C-peptide response of oral glucose compared with that of IV glucose, was reduced by approximately 50% in both obese youths with T2D and those with NGT compared with lean counterparts (obese T2D, 26%±6% vs. obese NGT, 29%±7% vs. lean NGT, 53%±4%). In line with this reduction in the incretin effect in T2D compared to obese subjects with NGT, a decrease of approximately 65% was seen in β-cell function in T2D subjects vs. lean subjects with NGT, as measured with a disposition index. These data show that, similar to adults, obesity is associated with a reduced incretin effect compared with lean individuals independent of glycemic status in adolescents. Even in individuals with T2D who have well-controlled glycemic status, a reduction in the incretin effect was still observed. We can therefore speculate that the incretin defect is present at an early stage of dysglycemia, together with β-cell dysfunction.
INCRETIN SECRETION

Despite a reduced incretin effect observed in subjects with T2D,\textsuperscript{50,52,54-58} compared to those with NGT, the etiology behind this phenomenon is unknown. There are conflicting findings in the literature regarding what happens to incretin secretion in T2D or IGT individuals. Some studies showed a significant decrease in incretin secretion,\textsuperscript{54,59,60} while others reported no differences between T2D/IGT vs. NGT subjects.\textsuperscript{50-52,55-58,61}

The following section describes studies that investigated incretin secretion in T2D and/or IGT subjects compared to NGT subjects. All studies quantified the incretin effect and secretion, unless otherwise noted.

Muscelli et al.\textsuperscript{54} evaluated incretin secretion in 24 NGT vs. 17 IGT adults vs. 10 T2D adults. GLP-1 secretion was reduced in T2D vs. NGT (2.0±0.5 nm vs. 4.1±2.3 nm, \(P=0.01\)), whereas GIP was similar between the two groups, suggesting that GLP-1 (but not GIP) contributes to the dysregulation of incretin effects in T2D vs. NGT subjects. Vilsbøll et al.\textsuperscript{59} investigated postprandial concentrations of incretins, both intact and total, during two different 3-hour mixed-meal tests in eight subjects with type 1 diabetes, eight lean and healthy subjects, eight obese subjects with T2D, and eight obese but otherwise healthy subjects. Individuals with type 1 diabetes were matched with lean and healthy counterparts with respect to age, sex and BMI; those with T2D were matched with obese with NGT. All meals consisted of the same foods and macronutrient percentage, but 1 meal was considered small at 260 kcal and the other large at 520 kcal. Meals were consumed on different days, in a random order, within a week of each other. Total GLP-1 was approximately 26\% lower in T2D subjects compared with obese subjects with NGT (2,627±237 pM vs. 3,553±427 pM, respectively) during the late phase (30 to 180 minutes) of the small meal. Intact GLP-1 was approximately 19\% lower in T2D vs. obese subjects with NGT (267±41 pM vs. 329±48 pM, respectively) in the early phase (0 to 30 minutes) of the small meal. Intact GIP did not differ among all four groups.

Similarly, Toft-Nielsen et al.\textsuperscript{60} evaluated GLP-1 secretion during a 4-hour mixed-meal test in 54 adult subjects with T2D, 15 with IGT, and 33 with NGT. GLP-1 secretion was reduced in T2D subjects compared with NGT (2,482±145 pM vs. 3,101±198 pM; \(p=0.024\)) and IGT (2,482±145 pM vs. 2,765±185 pM,
P = 0.011), even after controlling for BMI and sex. GIP secretion was similar in all three groups when corrected for BMI and sex. Collectively, a clear pattern of impairment in the GLP-1 secretion was established (Table 1), although more research is needed to clarify whether GIP secretion is a pathophysiological feature of T2D.

In contrast to the aforementioned studies, other studies in adults and youth were not able to identify statistically or clinically meaningful evidence (Table 2). Lee et al. investigated how incretin levels are associated with different stages of glucose intolerance in 12 NGT, 7 IGT and 21 T2D Japanese adults during a 2-hour OGTT and mixed-meal tolerance test. The mixed-meal tolerance test was 480 kcal, with a ratio for carbohydrates, proteins, and fats of 2.8:1:1. During the OGTT and mixed-meal tolerance test, intact GLP-1 and GIP secretion did not differ among the groups. No impairment in incretin secretion in T2D or IGT vs. NGT subjects was found in other studies (Table 2). However, Vilsbøll et al., Toft-Nielsen et al., and Lee et al. did not investigate the incretin effect. Furthermore, a meta-analysis of 22 trials involving 29 stimulation tests showed that, in 275 patients with T2D, the GLP-1 total response was similar to that of 279 NGT members of a control group as determined by peak plasma concentrations. A meta-analysis of GIP secretion in patients with T2D found similar results. No significant differences in peak plasma or GIP area under the curve (AUC) were reported in 23 trials involving 28 different stimulation tests of 363 T2D subjects vs. 325 NGT controls. The hypothesis that incretin secretion plays no significant role in the reduced incretin effect in T2D subjects compared to those with NGT is supported by the findings that hyperglycemia downregulates GLP-1R and GIPR. This is further supported by the observed inability of GIP to stimulate insulin in individuals with T2D. However, GLP-1 retains its insulinotropic potential in those with T2D. These studies reveal a pattern of reduced secretion of GLP-1, but not GIP. This suggests that both decreased GLP-1 secretion and a reduced insulinotropic effect of GIP can contribute to the reduced incretin effect observed in T2D subjects compared to those with NGT. Additional large cohort studies are needed to reach conclusive findings in this respect.
GLP-1RA STUDIES

GLP-1RAs have recently been marketed as a frontline therapy for patients seeking to manage T2D. The length of action for GLP-1RA varies, with lixisenatide and exenatide as the primary short-acting GLP-1RAs, and dulaglutide, albiglutide, liraglutide, and exenatide-LAR as the primary long-acting GLP-1RAs. The following section is broken into reviews of short-acting and long-acting GLP-1RA studies.

SHORT-ACTING GLP-1RA

Fonseca et al. evaluated the efficacy and safety of once-per day lixisenatide monotherapy in a 12-week randomized, double-blind, placebo-controlled, parallel-group trial of 361 adults not currently on glucose-lowering therapy agents. Patients were randomized into 1 of 4 regimens on a 1:1:1:1 ratio. Group 1 members received lixisenatide using a two-step dose increase, taking 10 mg for the first week, 15 mg for the second week, and 20 mg for the remaining weeks. Members of group 2 received lixisenatide using a single-step dose increase, taking 10 mg for the first 2 weeks and then 20 mg/wk. Groups 3 and 4 were the placebo groups and were placed into the same dose categories as group 1 and group 2, respectively. The primary end point was change in HbA1c levels from baseline to week 12. Patients given lixisenatide achieved an HbA1c level <7.0% (52% in the two-step and 47% in the single-step groups achieved the goal) and ≤6.5% (32% in the two-step and 25% in the one-step groups). The mean average of both lixisenatide groups was greater than the mean average of both placebo groups (26.8% and 12.5%, respectively; P<0.01). The results suggest a high efficacy for a once-daily administration of lixisenatide monotherapy with respect to the optimal glycemic control. Kendall et al. evaluated the effects of exenatide in 733 adults with T2D who were unable to achieve glycemic control with a metformin-sulfonylurea combination therapy in a 30-week, double-blind, placebo-controlled study in which HbA1c levels ranged from 7.5% to 11.0%, the metformin dose was ≥ 1,500 mg/day, and the sulfonylurea dose was at least the maximally effective dose for 3 months.
before screening. Participants were randomly assigned to a placebo group, arm A, or arm B. Members of both arms A and B began the study with a dose of 5 µg. After 4 weeks, arm B members were increased to 10 µg while the dose for those in arm A remained the same. The primary outcome measures were glycemic control as assessed by change in HbA1c. Both exenatide treatment arms were more likely to achieve an HbA1c ≤7% (34% [10 µg], 27% [5 µg], and 9% [placebo], P<0.0001) compared with the placebo. These data demonstrate the efficacy of exenatide treatment compared with placebo and suggest a dose-effective response to exenatide. Collectively, these clinical trials confirm the efficacy of short-acting GLP-1RA (with daily lixisenatide and exenatide injections) in lowering HbA1c.

**LONG-ACTING GLP-1RA**

Umpierrez et al.\(^7^1\) evaluated the efficacy and safety of once-weekly dulaglutide monotherapy compared with metformin in 807 adults with T2D in a 52-week double-blind trial. Patients were randomized into three groups: 1.5 mg dulaglutide, 0.75 mg dulaglutide, or metformin. All were progressively titrated up to 2,000 mg/day during the first 4 weeks of treatment or at least 1,500 mg/day depending upon tolerability. The effects of 1.5 mg and 0.75 mg dulaglutide on glycemic control were superior to those of metformin, with more participants in both dulaglutide groups achieving HbA1c targets of <7.0 and ≤6.5% (46% in the 1.5 mg group vs. 40% in the 0.75 mg group vs. 30% in the metformin group, P<0.05). The data suggest that dulaglutide is more efficacious at improving glycemic control compared with metformin. Tanaka et al.\(^7^2\) compared the efficacy and safety of liraglutide monotherapy with those of metformin in 46 overweight and obese Japanese adults with T2D and suboptimal glycemic control (HbA1c, 6.9%–9.4%) in a 24-week, randomized controlled trial. Participants were randomized into one of two groups. Participants in the liraglutide group received an initial dosage of 0.3 mg/day subcutaneously, with an up-titration of 0.3 mg weekly until reaching 0.9 mg/day. Participants in the metformin group took an initial dosage of 500 to 750 mg/day, with an up-titration to a 1,500 mg/day. The primary end point was change in HbA1c at week 24.
The reduction in HbA1c was similar between metformin and liraglutide. However, participants in the liraglutide group, compared with the metformin group, reached a rapid maximal reduction in HbA1c as measured by change in HbA1c at week 4 (−0.56%±0.36% vs. −0.31%±0.29%, *P*=0.02). The results indicate that metformin and liraglutide have similar effective glucose-lowering abilities as measured by HbA1c. Nauck et al.\textsuperscript{73} evaluated the efficacy and safety of weekly albiglutide monotherapy in 309 adults with T2D in a 52-week randomized, double-blinded, placebo-controlled trial in which patients received 30 mg (n=102) or 50 mg (n=102) of albiglutide once-weekly, or a matching placebo (n=105). Participants had HbA1c levels that were inadequately controlled by exercise and diet (HbA1c ≥7% and ≤10%) and were not using glucose-lowering agents. The primary efficacy of the treatment in controlling HbA1c from baseline to week 52 was superior in the albiglutide 30 mg and 50 mg groups compared with placebo groups, with a dose-response relationship between the dose of albiglutide and changes in HbA1c of −0.84% in the 30 mg group vs. −1.04% in the 50 mg group (*P*<0.001). These data suggest albiglutide is a safe and effective monotherapy to lower HbA1c, compared with placebo, for subjects with T2D. Last, in a 26-week, double-blind, randomized controlled trial, Russell-Jones et al.\textsuperscript{74} evaluated the efficacy and safety of exanatide once-weekly compared with metformin, pioglitazone, and sitagliptin in 820 drug-naïve adults with T2D. Group 1 members received 2 mg of subcutaneous exanatide+oral placebo (n=248), members of group 2 received 2,000 mg/day of metformin+subcutaneous placebo (n=246), members of group 3 received 45 mg/day of pioglitazone+subcutaneous placebo (n=163), and group 4 consisted of subjects who received 100 mg/day of sitagliptin+subcutaneous placebo (n=163). The primary aim was to assess the efficacy of exanatide compared with metformin, pioglitazone, and sitagliptin, as measured by change in HbA1c after 26 weeks. Subjects who received exanatide experienced significantly reduced HbA1c levels compared to those received sitagliptin (−1.53% vs. −1.15%, *P*<0.01). However, no difference was found when compared with the subjects treated with metformin or pioglitazone. Taken together, growing clinical evidence suggests that GLP-1RA can effectively lower glycemic values when compared with placebo and that it is as effective as metformin.
Most previous studies focusing on GLP-1RA were performed exclusively in adults, and evidence that GLP-1RA would have similar glucose-lowering effect in youths is lacking. Tamborlane et al.\textsuperscript{17} examined the efficacy of liraglutide compared with placebo in 135 youths with T2D who had an inadequate response to metformin (HbA1c >7% and<11%), with or without insulin. Patients were randomly assigned at a 1:1 ratio to receive either subcutaneous liraglutide or placebo for 26 weeks in combination with metformin, with or without basal insulin, combined with a diet and exercise regimen. The initial dose of liraglutide was 0.6 mg per day, escalated in both groups by approximately 0.6 mg each week over 2 to 3 weeks. The primary outcome was change from baseline in HbA1c at week 26. Members of the liraglutide group had a reduction of 0.64% in HbA1c compared with an increase of 0.42% in the placebo group, with an estimated treatment difference of −1.06% \((P<0.001)\). A greater percentage of participants in the liraglutide arm reached HbA1c <7% compared with the placebo group (63.7\% vs. 36.5\%, \(P<0.001\)). This study indicates liraglutide is as effective in adolescents as in adults at reducing HbA1c compared with placebo.

Despite an increase in heart rate,\textsuperscript{75,76} GLP-1RA has consistently demonstrated cardiovascular safety for individuals with T2D based on observations of no further alteration of the rate of major cardiovascular or other adverse events after the addition of GLP-1RA to typical diabetes care.\textsuperscript{77} GLP-1RA may even be protective against future cardiovascular events, as liraglutide was associated with a significant reduction in major cardiovascular events compared with placebo in adults with T2D.\textsuperscript{75} It is unclear if this is also the case for adults with NGT and youths with T2D, suggesting further investigations in a variety of patients are required.

**GLP-1RA FOR WEIGHT LOSS**

Evidence has emerged that GLP-1RA can be used as a weight-loss agent for overweight and obese individuals without T2D. Rubino et al.\textsuperscript{78} examined the weight-loss effects of weekly semaglutide vs.
placebo in 803 overweight or obese individuals without T2D. After a 20-week run-in period (16 weeks of dose escalation followed by 4 weeks of a maintenance dose), participants were randomized 2:1 to either 2.4 mg/week of semaglutide or placebo, with lifestyle intervention in both groups. Change in body weight from week 20 to 68 was the primary end point and subjects in the semaglutide arm lost a greater percentage of their body weight compared with those in the placebo arm (−7.9% vs. +6.9%; P<0.001). Furthermore, a larger percent of subjects lost more than 20% of their body weight in the semaglutide arm than in the placebo arm (39.6% vs. 4.8%). In line with this, Wadden et al. examined the weight-loss effects of once-daily liraglutide (3.0 mg) compared with placebo in adults without T2D who had already lost more than 5% of their body weight by adhering to a low-calorie diet. One of the primary end points was percentage weight change from randomization. Members of the liraglutide arm lost an additional 6.2% of body weight compared with a 0.2% loss for those in the placebo arm. Furthermore, 50.5% of individuals in the liraglutide group lost more than 5% of body weight compared with 21.8% of individuals in the placebo group (all P<0.001).

As has been reported for adults, liraglutide has also proven efficacious as a weight-loss agent in obese adolescents. Kelly et al. examined the weight-loss effects of once-daily liraglutide (3.0 mg) compared with placebo in 125 obese adolescents who had a poor response to lifestyle therapy alone. The primary end point was change from baseline BMI standard-deviation score at week 56. Subjects in the liraglutide arm experienced a greater reduction compared to those in the placebo arm (−0.23±0.05 vs. −0.00±0.05; estimated difference, −0.22; P=0.002). These clinical trials highlight the efficacy of GLP-1RA as a potential weight-loss therapeutic in both obese adults and obese adolescents.

**FUTURE DIRECTIONS**

GIP has previously been considered an undesirable pharmacological agent for treatment of T2D, due to the absence of insulinotropic effects derived from GIP (while its glucagonotropic action is retained).
However, the two agonists have been explored through co-administration as a potential T2D therapeutic. LY3298176 (tirzepatide), a novel dual GIPR/GLP-1R agonist, has recently attracted attention for its glycemic and weight-reducing effects. Frias et al.\textsuperscript{83} examined the efficacy of tirzepatide compared with placebo and dulaglutide in 316 adults with a BMI of 23 to 50 kg/m\(^2\) and T2D that was inadequately controlled by diet and exercise alone (HbA1c levels of 7.0% to 10.5%), or by stable metformin therapy. Patients were randomized 1:1:1:1:1:1 to receive once-weekly subcutaneous tirzepatide (1, 5, 10, or 15 mg), dulaglutide (1.5 mg), or placebo. The primary outcome was change in HbA1c from baseline to week 26. Those treated with tirzepatide saw a dose-dependent response reduction (−1.06%, −1.75%, −1.89%, and −1.94%, respectively). All tirzepatide arms saw a greater HbA1c reduction compared with the placebo arm (\(P<0.001\)), while only those treated with tirzepatide 5, 10 and 15 mg saw a greater HbA1c reduction compared with dulaglutide (−1.21%, \(P<0.05\)). Weight reduction was also dose-dependent (−0.9, −4.8, −8.7, and −11.3 kg, respectively). Only tirzepatide treatments of 5, 10, and 15 mg were associated with a significant weight reduction compared with placebo (\(P<0.05\)), while 10 and 15 mg doses produced greater response compared with dulaglutide (−2.7 kg, \(P<0.0001\)). These data suggest that tirzepatide can be used as an effective glycemic and weight-loss therapeutic agent in adults. While this is promising, it is important to note that this was a phase 2 trial. Further studies should compare the efficacy and safety of tirzepatide with that of other GLP-1RAs and other glucose-lowering therapeutics, such as metformin and insulin.

**CONCLUSIONS**

It is now clear that incretins play a role in the pathophysiology of T2D. In both adults and adolescents, a clear decrease in the incretin effect has been reported in individuals with T2D, especially when compared with normoglycemic counterparts. However, findings on incretin secretion in adults with T2D compared with those with NGT have been inconsistent, requiring continuous efforts to replicate and/or collect concordant evidence. To our knowledge, all studies looking at incretin secretion have been cross-sectional.
The absence of longitudinal research makes it difficult to determine the specific pathophysiological role of incretin hormone dysregulation in the development of T2D. Different methodological approaches have been used to assess the incretin effect and its absolute secretion, possibly contributing to the discrepancies noted in this review. Michaliszyn et al. calculated the incretin effect as the ratio of OGTT-βCGS to the 2-hour hyperglycemic clamp-βCGS, while Nauck et al. quantified the incretin effect by measuring the insulin response to oral glucose compared with the response to IV glucose. Both studies showing a reduced incretin effect in subjects with T2D vs. those with NGT, but the extent of the reduction differed. There are also differences in how incretin secretion is measured. Seven studies reported on total incretin secretion, 2 reported on active secretion, a single on both, and 1 did not specify which was used. Both meta-analyses reported on total incretin secretion. It is possible that only active GLP-1 and GIP secretion are relevant to the incretin effect, as once DPP-4 shortens the incretins, they no longer have insulinotropic actions.

In addition to the methodological concern, race and/or ethnic differences in incretin physiology may contribute to these discrepancies. A review by Cho of incretin physiology and pathophysiology in Asians found that East Asians with T2D do not experience a reduced incretin effect compared with those with NGT. It would be useful to investigate whether there is a racial or ethnic element of incretin profiles in adults and youths who are at highest risk for T2D. Another confounding variable is the effect of metformin, which has been shown to increase GLP-1 levels. It is unclear what effect, if any, this has, because metformin’s effect on the incretin effect is unknown. Metformin does not increase insulin secretion, and it does not appear that this would affect the incretin effect. Metformin’s main mechanism of action involves lowering hepatic glucose output by inhibiting complex 1 in the electron transport chain. To this point, Michaliszyn et al. have not observed any differences in fasting GLP-1, 2-hour GLP-1, or GLP-1 incremental AUC between youths with T2D prescribed metformin and those who were not. However, through indirect mechanisms, metformin may influence the incretin effect. Metformin’s ability to lower blood glucose could lessen the chance that GLP-1R and GIPR can be downregulated by hyperglycemia.
therefore decreasing the reduction of the incretin effect typically seen in patients with T2D. Incretin resistance in \( \beta \)-cells may be a contributing factor, analogous to insulin resistance in peripheral tissue.\(^5\)

Among available anti-diabetic therapies, GLP-1RAs have demonstrated promising efficacy in diabetic patients.\(^1\)\(^9\) Further research is needed in youths, as the only FDA-approved GLP-1RA for youths is liraglutide.\(^1\)\(^7\) Evidence points to GLP-1RA drugs as potential monotherapies for treatment of T2D.\(^6\)\(^8\),\(^7\)\(^1\)\(^7\)\(^-\)\(^7\)\(^4\) Currently, metformin is the American Diabetes Association’s preferred first-line therapy for treatment of T2D.\(^8\)\(^9\) Despite its efficacy in adults and low cost,\(^9\) metformin has a low success rate, as measured by glycemic control and restoration rate of \( \beta \)-cell function in youths. Additional trials should be conducted to determine if GLP-1RA can replace metformin as a first-line defense for youths and/or adults with T2D.

Trials comparing GLP-1RA to metformin have produced only mixed results, with 1 trial showing a higher percentage of participants reaching their HbA1c goals (<7%) with GLP-1RA,\(^7\)\(^1\) and others showing no difference.\(^7\)\(^2\),\(^7\)\(^4\) More trials are needed to determine the role GLP-1 and GIP co-agonists can play in T2D therapeutic options. While tirzepatide has promise, more clinical trials are needed in both adult and adolescents.

In summary, incretins appears to be a key pathophysiological risk factor for T2D and are promising targets of treatments for T2D, cardiovascular disease, and obesity. Additional research in large cohorts and prospective observations are warranted to confirm the role of incretin and its effects in both adults and youths at higher risk for T2D and/or those with T2D.

**CONFLICTS OF INTEREST**

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: ***; acquisition of data: ***; analysis and interpretation of data: ***; drafting of the manuscript: ***; critical revision of the manuscript: ***; statistical analysis: ***; obtained funding: ***; administrative, technical, or material support: ***; and study supervision: ***.
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**Table 1.** Studies reporting significant differences in absolute incretin hormone response between individuals with and without T2D

| Study            | Participant | Measure            | Active or total GLP-1 | Primary finding                                                                 |
|------------------|-------------|--------------------|-----------------------|---------------------------------------------------------------------------------|
| Muscelli et al.  | T2D (n=10), IGT (n=17), NGT(n=24) | OGTT, IV glucose administration | Total GLP-1 | GLP-1 was reduced in T2D vs. NGT during an OGTT (2.0±0.5 nm vs. 4.1±2.3 nm; P=0.01). No difference was found in GIP. |
| Vilsbøll et al.  | Diabetic patients (n=8), lean, healthy controls (n=8), obese individuals (n=8), obese T2D patients (n=8) | Mixed-meal challenge | Both | Total late phase GLP-1 was reduced compared to lean (2,627±237 pM vs. 2,685 ±114 pM; P<0.02) and intact during early phase (267±4 pM vs. 416±98 pM; P=0.04) during the small meal. No significant difference was found in GIP. |
| Toft-Nielsen et  | T2D (n=54), IGT (n=15), NGT (n=33) | Mixed-meal challenge | Active | GLP-1 was reduced in T2D vs. NGT (2,482±145 pM vs. 3,101±198 pM; P=0.024). GIP in T2D was not significantly reduced when corrected for BMI and sex. |

T2D, type 2 diabetes; GLP-1, glucagon-like peptide-1; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; IV, intravenous; GIP, glucose-dependent insulinotropic polypeptide; BMI, body mass index.
### Table 2. Studies reporting not significant differences in absolute incretin hormone response between individuals with and without T2D

| Study            | Participant                                                                 | Measure                                                                 | Active or total GLP-1                                                                 | Primary finding                                                                                           |
|------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Knop et al.      | Chronic pancreatitis+diabetes (n=8), chronic pancreatitis and NGT (n=8), T2D (n=8), healthy controls (n=8) | OGTT, IV Total GLP-1 glucose administration                             | GLP-1 did not differ between groups. GIP was highest in CP+diabetes compared to CP+NGT, T2D, and healthy control (10.6±2.0 nm, 7.7±2.3 nm, 5.4±0.5 nm, 6.3±1 nm; P<0.05). |
| Nauck et al.     | T2D (n=14), healthy controls (n=8)                                           | OGTT, IV NA GLP-1 glucose administration                               | There was no statistical difference in GIP secretion compared in both groups. GLP-1 was not measured.     |
| Knop et al.      | Obese T2D (n=8), obese NGT (n=8), lean T2D (n=8), lean NGT (n=8)             | OGTT, IV Total GLP-1 glucose administration                             | GLP-1 did not differ between groups. GIP was shown to be increased in both obese groups compared to lean groups (obese T2D, 17.0±2.0 pM; obese NGT, 13.9±1.2 pM; lean T2D, 10.6±1.2 pM; lean NGT, 9.8±0.9 pM; P<0.05). |
| Lee et al.       | T2D (n=21), IGT (n=7), NGT (n=12)                                            | OGTT, mixed-meal challenge Active GLP-1 or GIP                           | GLP-1 or GIP did not differ between groups during OGTT and MMT                                |
| Michaliszyn et al. | 255 Obese youth individuals, T2D (n=34), IGT (n=48), NGT (n=173)           | OGTT, IV Total GLP-1 glucose administration                             | GLP-1 was highest in T2D, followed by NGT and IGT during the late phase (326.0±42.9 pM, 105.6±19.0 pM, 67.7±36.1 pM; P=0.005). No difference in GIP was found between all three groups. |
| Yeow et al.      | Youth T2D (n=25), healthy controls (n=15)                                    | OGTT, IV Total GLP-1 glucose administration                             | GLP-1 did not differ between groups, GIP was not collected.                                    |
| Muscelli et al.  | IGT (n=10) NGT (n=11)                                                         | OGTT, IV Total GLP-1 glucose administration                             | GLP-1 was reduced ~25% in IGT vs. NGT, but not GIP.                                            |
| Aulinger et al.  | Obese T2D (n=10), obese NGT (n=11), lean NGT (n=8)                           | OGTT, IV Total GLP-1 glucose administration                             | No difference in GLP-1 or GIP                                                                 |

T2D, type 2 diabetes; OGTT, oral glucose tolerance test; IV, intravenous; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; CP, chronic pancreatitis; NGT, normal glucose tolerance; NA, not available; MMT, ***; IGT, impaired glucose tolerance.
Table 3. Studies of short-acting GLP-1RA

| Author               | Population                                                                 | Comparison group                                          | Key finding                                                                 |
|---------------------|-----------------------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------|
| Fonseca et al.      | 361 Adults not on glucose-lowering agents; mean age (53.7 yr), mean BMI (31.9 kg/m²), mean duration since diagnosis (1.3 yr), race (263 white, 80 Asians, 6 black, 12 other), sex (186 male, 175 female) | Lixisenatide two-step dose (10 mg for the first week, 15 mg for the second week, 20 mg for remaining weeks) vs. 1-step (10 mg for the first 2 weeks, 20 mg for remaining weeks) vs. two placebo arms (same doses categories as lixisenatide) | Patients administered lixisenatide achieved a HbA1c <7.0% and ≤6.5% significantly more than the placebo group (26.8% and 12.5%, respectively; P<0.01). |
| Kendall et al.      | 733 Adults unable to achieve glycemic control; mean age (55.3 yr), mean BMI (33.7 kg/m²), mean duration since diagnosis (8.9 yr), race (498 white, 83 black, 18 Asians, 3 Native American, 118 Hispanic, 13 other), sex (426 male and 307 female) | Arm A (5 µg) vs. Arm B (5 µg for the first 4 weeks, then 10 µg for the remaining weeks) vs. placebo | Arm A and Arm B exanatide treatment arms were more likely to achieve HbA1c ≤7% (34 [10 µg], 27 [5 µg], and 9% [placebo]; P<0.0001) compared with placebo. |

GLP-1RA, glucagon-like peptide-1 receptor agonists; BMI, body mass index; HbA1c, glycosylated hemoglobin.
Table 4. Studies of long acting GLP-1RA

| Author          | Population                                      | Comparison group                                                                 | Key finding                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Umpierrez et al. | 807 Obese adults; mean age (55.7 yr), mean      | 1.5 mg dulaglutide vs. 0.75 mg dulaglutide vs. metformin                         | The HbA1c-lowering effects subcutaneous and non-subcutaneous dulaglutide were superior to metformin in patients achieving their HbA1c targets of <7.0% and ≤6.5% (1.5 mg, 46; 0.75 mg, 40; and metformin, 30%; P<0.05). At the end of the study, reduction in HbA1c was similar in both groups. |
|                 | BMI (33.3 kg/m²), mean duration since diagnosis (3 yr), race (600 white 85 native American, 61 Asians, 53 black, 7 multiple races, 1 Hawaiian), sex (353 male and 454 female). | (progressively titrated up to 2,000 mg/day during the first 4 weeks of treatment or at least 1,500 mg/day depending upon tolerability). Liraglutide (starting at 0.3 mg/day subcutaneously, with an up-titration of 0.3 mg weekly until the participant reached 0.9 mg/day) vs. metformin (starting at an initial dose of 500 to 750 mg/day, with an up-titration to a 1,500 mg/day) |                                                                                                                                             |
| Tanaka et al.    | 46 Japanese adults with suboptimal glycemic      | Albiglutide 50 mg vs. albiglutide 30 mg vs. placebo                             | Patients taking 30 mg and 50 mg albiglutide experienced superior reductions in HbA1c compared to the placebo group (−0.84% vs. −1.04% respectively, P<0.001).                                                |
|                 | control. Mean age (52.9 yr), mean BMI (28.7 kg/m²), mean duration since diagnosis (5.1 yr), race (46 Asians), sex (29 male and 17 female). | vs. placebo                                                                       |                                                                                                                                                                                                             |
| Nauck et al.     | 309 Adults not using glucose lowering agents.   | Exenatide (EQW) (2 mg)+oral placebo vs. 2,000 mg/day metformin+subcutaneous placebo vs. 45 mg/day pioglitazone+subcutaneous placebo vs. 100 mg/day of sitagliptin+subcutaneous placebo | Exanatide significantly reduced HbA1c compared to sitagliptin (−1.53 vs. −1.15%, P<0.01), respectively. However, no significant difference when compared to metformin or pioglitazone. |
|                 | Mean age (52.9 yr), mean BMI (33.5 kg/m²), mean duration since diagnosis (3.9 yr), race (242 white, 38 black, 7 Asians), sex (166 male and 135 female). | vs. placebo                                                                       |                                                                                                                                                                                                             |
| Russell-Jones et al. | 820 Drug-naive adults. Mean age (53.8 yr), mean BMI (31.2 kg/m²), mean duration since diagnosis (2.67 yr), race (552 white, 173 Asians, 65 Hispanic, 25 African, 5 other), sex (484 male and 336 female). | Exenatide (EQW) (2 mg)+oral placebo vs. 2,000 mg/day metformin+subcutaneous placebo vs. 45 mg/day pioglitazone+subcutaneous placebo vs. 100 mg/day of sitagliptin+subcutaneous placebo | Exanatide significantly reduced HbA1c compared to sitagliptin (−1.53 vs. −1.15%, P<0.01), respectively. However, no significant difference when compared to metformin or pioglitazone. |

GLP-1RA, glucagon-like peptide-1 receptor agonists; BMI, body mass index; HbA1c, glycosylated hemoglobin; EQW, ***.