The Physiologic Role of Incretin Hormones: Clinical Applications

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Traditionally, the treatment of type 2 diabetes mellitus (T2DM) involves a progression of phases, from conventional lifestyle interventions to monotherapy, to combination therapy involving oral agents and insulin initiation, and its use either alone or with oral pharmacotherapy. Currently, the need for antidiabetic therapies with fewer adverse effects (e.g., weight gain, reduced rates of hypoglycemia) remains unmet. In addition, most treatments fail to adequately control postprandial hyperglycemia. Traditional options have generally been directed at the "insulin demand" aspect and have targeted insulin secretion or insulin resistance in peripheral tissues. Only recently have agents been available to address the "glucose supply" aspect that leads to fasting hyperglycemia in patients with T2DM. Incretin-based therapies, however, address both aspects. Two classes of incretin-directed therapies are available and work by either increasing endogenous levels of glucagon-like peptide-1 (GLP-1) (e.g., dipeptidyl peptidase-4 inhibitors) or by mimicking the activity of endogenous GLP-1 (e.g., GLP-1 agonists). These therapies treat the key metabolic abnormalities associated with T2DM but do so with reduced rates of hypoglycemia and do not promote weight gain as compared with conventional therapies.
have mechanisms that do not adequately control postpranacial glucose. Specifically, conventional therapies may have mechanisms that increase insulin secretion, provide effective insulin levels, or increase sensitivity in the peripheral tissues (ie, skeletal muscle and adipose tissue). In other words, these agents may address only the "insulin demand" component of diabetes. Thus, the deficits in insulin activity needed for the uptake, storage, and utilization of glucose have been addressed by traditional therapies.

However, diabetes mellitus is not only associated with insufficient insulin response to glucose but also overproduction of glucose from the liver, which results from an inability to fully suppress glucagon. As a result, the liver continues to produce glucose, resulting in both fasting and postprandial hyperglycemia. If an imbalance exists between the supply of glucose and the amount of glucose utilization and disposal, glucose dysregulation and T2DM result.

The relationship between hepatic glucose production (HGP) and fasting plasma glucose (FPG) has been established for many years. For example, patients with T2DM (n=77), when compared to nondiabetic controls (n=72), had a higher FPG (162 vs 92 mg/dL, respectively; P<.001) as well as a higher level of basal HGP (2.17 vs 1.84 mg/kg/min, respectively; P<.001). A statistically significant, positive correlation (r=0.847; P<.001) was also observed between the rate of basal HGP and FPG in the diabetic group.

The level of HGP is related to basal glucagon production. As such, studies that were designed to suppress plasma glucagon using somatostatin analogues in patients with T2DM demonstrated that HGP levels can be reduced significantly. Glucagon was responsible for maintaining 58% of basal HGP in subjects with T2DM in the presence of basal insulin. These results demonstrate that the level of basal FPG in diabetes mellitus is related to the level of basal HGP, which is regulated by the glucagon insulin axis. These results thus demonstrate the importance of not only insulin but also glucagon in the pathogenesis of T2DM, and provide a framework for the further understanding of gastrointestinal hormones (ie, incretins) as well as the use of incretin-based therapies in the management of T2DM.

**Physiologic Role of Incretins**

The incretin effect refers to the observation that a difference in plasma insulin response to glucose occurs when equimolar levels of glucose are achieved through either oral or intravenous administration. Up to 70% of the insulin response after a glucose load may be caused by the effects of incretins, or gut-derived hormones, which mediate the insulinotropic response. The two major incretin hormones in humans are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are secreted by intestinal cells. Both incretin hormones are released in response to ingestion of glucose.

Studies have further demonstrated that, in patients with T2DM, the incretin effect is attenuated, which suggests a deficit in incretin action. Indeed, the two major incretins, particularly GLP-1, have biologic activities that are related to key pathophysiologic characteristics of T2DM. Both GLP-1 and GIP are known to stimulate insulin secretion and have been shown to promote expansion of β-cell mass; GLP-1 has also been shown to inhibit glucagon secretion.

Loss of β-cell mass is known to occur with progression from impaired glucose tolerance to T2DM, while the lack of suppressed glucagon in patients with T2DM results in relative glucagon hypersecretion and excess HGP. Thus, several key abnormalities characteristic of T2DM appear to be related to the functions of incretins, particularly GLP-1. These findings support the role of incretins in T2DM and demonstrate the potential of incretin-based agents as therapy.

**Incretins as T2DM Therapy**

Studies have investigated the use of the incretins GLP-1 and GIP to restore insulin response in obese patients with and without T2DM. In one representative study, plasma insulin was measured before and after glucose administration in patients with T2DM and healthy volunteers. As expected, the insulin response in patients with T2DM was decreased compared with normal subjects. Administration of GLP-1 to patients with T2DM was observed to lead to a significant increase in the glucose-dependent insulin response compared to GIP administration. When levels of plasma glucagon in response to glucose (hyperglycemic clamp) were examined in healthy patients and obese patients with T2DM, glucose infusion without incretins caused a marked decrease in glucagon secretion in healthy subjects compared with fasting level, whereas the response was attenuated in patients with obesity. Notably, however, the administration of GLP-1 appeared to have a greater suppression of glucagon levels compared with GIP administration, demonstrating enhanced efficacy of GLP-1 on glucagon suppression in the obese patients with T2DM.

Placebo-controlled studies have also demonstrated that infusion of GLP-1 in fasting patients with T2DM significantly reduces plasma glucose levels, restores the insulin secretory response, and suppresses plasma glucagon levels compared with placebo (Figure 1). These studies confirmed that GLP-1 is capable of enhancing both insulin secretion and glucagon suppression in response to glucose in patients with T2DM. Importantly, the action of GLP-1 has the benefit of glucose dependence, so that insulin is not overproduced. Thus, incretin therapy should markedly improve normal islet physiologic responses in α cells (glucagon response) and β cells (insulin response).

Use of GLP-1 as a practical incretin therapy in patients with T2DM, however, requires an understanding of its normal secretion and metabolism, which is outlined schematically in Figure 2. In response to a meal, GLP-1 is released predominantly in its active form, GLP-1 (7-36), and rapidly metabolized to an inactive form, GLP-1 (9-36), by the enzyme dipeptidyl peptidase-4 (DPP-4). Because of the rapid inactivation of GLP-1 in vivo and the short half-life, it may be necessary to continuously infuse GLP-1 into patients with T2DM to maintain an effect. However, continuous infusion as a means to deliver therapy is pharmacologically inefficient and clini-
cally impractical. Development of incretin-based therapies has, therefore, required modulation of its secretion and metabolic pathways using at least two distinct strategies. Specifically, therapeutic agents have been developed that either inhibit the enzyme DPP-4 (DPP-4 inhibitors), which subsequently increases endogenous GLP-1, or consist of a GLP-1 peptide molecule that prevents breakdown by DPP-4 in vivo (GLP-1 agonists).

**DPP-4 Inhibitors**

Studies on DPP-4 inhibitors sitagliptin phosphate and saxagliptin, oral agents that increase endogenous GLP-1 by inhibiting the activity of the enzyme DPP-4 (DPP-4 inhibitors), which subsequently increases endogenous GLP-1, or consist of a GLP-1 peptide molecule that prevents breakdown by DPP-4 in vivo (GLP-1 agonists), has been demonstrated to have efficacy when used as monotherapy. When used in combination with metformin, sitagliptin provided a comparable degree of glycemic control (assessed by HbA1c levels) as glipizide (Figure 3). In a 52-week, randomized, noninferiority trial, patients with inadequate glycemic control on metformin were randomly assigned to receive combination therapy with the addition of either sitagliptin (n=382) or glipizide (n=411). The mean change from baseline in HbA1c in both groups was 0.67% in the per-protocol analysis, which demonstrated identical efficacy in glycemic control for these two agents when combined with metformin. Moreover, sitagliptin demonstrated better safety compared to glipizide when used with metformin: whereas weight increased on glipizide (+1.1 kg), a statistically significant decrease in body weight (-1.5 kg) was demonstrated with sitagliptin (P<.001) (Figure 4). In general, however, DPP-4 inhibitors have been demonstrated to be weight-neutral. In addition, there was a significantly lower incidence of hypoglycemia with sitagliptin (Figure 4). The studies comparing the DPP-4 inhibitor to glipizide on a background of metformin therapy clearly show the potential advantages by demonstrating comparable efficacy as sulfonylureas but less hypoglycemia and more favorable effects on weight. Studies have also demonstrated that initial combination of sitagliptin and metformin in a single combination pill is also very effective in reducing glycemia and improving markers of β-cell function. Sitagliptin has also been shown to be beneficial when combined with thiazolidinediones.

Similar results have been observed in studies of other DPP-4 inhibitors. Saxagliptin has been shown to promote sustained glycemic control over 102 weeks when used with metformin in patients with T2DM inadequately con-
trolled with metformin alone.\textsuperscript{22,23} Once-daily saxagliptin monotherapy in drug-naïve patients with T2DM reduced HbA\textsubscript{1c} by -0.43\%, -0.46\%, and -0.54\% relative to placebo at doses of 2.5 mg, 5 mg, and 10 mg, respectively. Reductions in HbA\textsubscript{1c} were observed in all saxagliptin dose cohorts as early as week 4, reached a maximum at approximately week 8, and were maintained throughout the remaining 16 weeks of the study.\textsuperscript{23}

Initial combination therapy with saxagliptin (5 mg or 10 mg) plus metformin reduced HbA\textsubscript{1c} by -2.5\% at 24 weeks compared with -1.7\% and -2.0\% for saxagliptin 10 mg and metformin monotherapy, respectively.\textsuperscript{24} Saxagliptin as add-on therapy to metformin reduced HbA\textsubscript{1c} by -0.73\%, -0.83\%, and -0.72\% relative to placebo at doses of 2.5 mg, 5 mg, and 10 mg once daily, respectively, at 24 weeks.\textsuperscript{25} The addition of saxagliptin 2.5 mg or 5 mg in patients treated with a submaximal dose of glyburide (7.5 mg/d) reduced HbA\textsubscript{1c} by -0.54\% and -0.64\%, respectively, compared to patients treated with up titration of glyburide to 15 mg per day alone.\textsuperscript{26} Similar to other DPP-4 inhibitors, saxagliptin is well-tolerated, does not increase hypoglycemia, and is weight-neutral.\textsuperscript{27}

Alogliptin has also demonstrated efficacy in glycemic control when used in combination with metformin (week 26 change in HbA\textsubscript{1c}: -0.19\%, -0.66\%, and -0.80\% for placebo, alogliptin 12.5 mg, and alogliptin 25 mg, respectively [P<.001, both doses vs placebo]);\textsuperscript{28} and when used with insulin in patients with inadequately controlled T2DM by insulin alone or with metformin (week 26 change in HbA\textsubscript{1c}: -0.13\%, -0.63\%, and -0.71\% for placebo, alogliptin 12.5 mg, and alogliptin 25 mg, respectively [P<.001, both doses vs placebo]).\textsuperscript{29} The results for glycemic control were similar regardless of the background therapy.

These findings demonstrate the benefits of using incretin-based therapies, as glycemic control is comparable with that of other agents and can be readily achieved. In addition, the adverse effects of weight gain and hypoglycemia are markedly reduced when compared to conventional T2DM therapies. The most common adverse effects associated with DPP-4 inhibitors are upper respiratory infections, nasopharyngitis, headache, and urinary tract infections.\textsuperscript{31}

Thus, these data demonstrate the efficacy of DPP-4 inhibitors as therapeutic agents, particularly when used as a component of combination therapy, as well as the importance of incretin-directed therapy in addressing the metabolic abnormalities associated with T2DM.

**GLP-1 Agonists**

Increased GLP-1 activity in patients with T2DM can also be accomplished by modifying the GLP-1 peptide molecule itself to prevent breakdown by DPP-4 (Figure 2). This therapy is different from oral DPP-4 inhibitors in that it is injectable and can achieve pharmacologic levels of GLP-1 activity by providing a known

![Figure 3. Glycated hemoglobin (HbA\textsubscript{1c}) levels over time in patients receiving ongoing metformin therapy with either sitagliptin (100 mg daily) or glipizide. *Per protocol analysis; -0.51\% and -0.56\% for sitagliptin and glipizide, respectively, in last observation carried forward analysis. Source: With kind permission from Springer Science+Business Media: Adapted from Nauck MA et al. Diabetes Obes Metab. 2007;9(2):194-205.\textsuperscript{19}](http://jaoa.org/pdfaccess.ashx?url=/data/journals/jaoa/932119/)

![Figure 4. Changes in (A) body weight and (B) incidence of hypoglycemia in patients receiving ongoing metformin therapy with either sitagliptin (100 mg daily) or glipizide. Source: With kind permission from Springer Science+Business Media: Adapted from Nauck MA et al. Diabetes Obes Metab. 2007;9(2):194-205.\textsuperscript{19}](http://jaoa.org/pdfaccess.ashx?url=/data/journals/jaoa/932119/)
agonist of GLP-1. The DPP-4 inhibitor agents, by contrast, are directed at restoring endogenous levels of GLP-1.

Exenatide was the first commercially available GLP-1 agonist and has many years of clinical use. In pivotal studies, administration of the GLP-1 agonist exenatide to subjects on oral therapy with sulfonylureas, metformin, or both resulted in significant improvements in glycemic control over placebo from baseline in 30 weeks, as assessed by HbA1c (mean [SE], -1.1% [0.1%]), and also over a 3-year, open-label, uncontrolled extension period (-1.0% [0.1%]). Patients who completed 3 years of exenatide treatment also had reduced FPG (-23.5 mg/dL) and body weight (-5.3 kg). The corresponding percentage of patients achieving an HbA1c of 7.0% or less at the 30-week and 3-year intervals was 54% and 46%, respectively, while 30% of 3-year completers in the study achieved an HbA1c of 6.5% or less. Thus, exenatide therapy for at least 3 years produced a sustained and clinically relevant improvement in glycemic control and progressive weight reduction.

Results with another GLP-1 agonist, liraglutide, also demonstrated good efficacy in glycemic control. In the Liraglutide Effect and Action in Diabetes (LEAD) study, liraglutide resulted in sustained HbA1c control when used as a monotherapy in subjects with early stage T2DM who were either drug naive (previously on diet modification and exercise therapy) or previously treated with oral therapy at up to 50% of the maximum dose. At week 52, liraglutide 1.2 mg and 1.8 mg decreased HbA1c levels by -0.84% and -1.14%, respectively. These reductions were significantly greater than those seen with the comparator, glimepiride (-0.51%).

Other clinical trials in the LEAD program demonstrated efficacy of liraglutide in glycemic control when used as add-on therapy. In combination with a sulfonylurea, liraglutide in 1.2-mg and 1.8-mg doses resulted in an HbA1c decrease of -1.1% from baseline after 26 weeks, relative to either placebo (+0.2%; P < 0.0001) or rosiglitazone maleate (+0.4%; P < 0.0001). As add-on therapy to metformin, liraglutide 1.2 mg and 1.8 mg were superior to metformin monotherapy and were noninferior to combination therapy with metformin and glimepiride.

Similar results were observed when liraglutide was added to both metformin and rosiglitazone; after 26 weeks, mean HbA1c decreased by -1.5% with either dose of liraglutide compared to -0.5% with placebo. When compared to insulin glargine as add-on therapy to metformin and glimepiride, liraglutide resulted in an HbA1c reduction of -1.33% after 26 weeks, which was significantly greater than that seen with insulin glargine (-1.09%) or placebo (-0.24%) (P < 0.05). The authors reported that while a statistically significant difference vs insulin glargine was observed, they were unsure of the clinical relevance.

Available evidence from studies of incretin-based therapies using the GLP-1 agonist demonstrates identical glycem ic control when compared with conventional agents. However, as with the DPP-4 inhibitors, there is a difference in terms of the adverse event profile. In a randomized, open-label crossover study of patients with T2DM receiving metformin or a sulfonylurea, eligible patients were randomly assigned to receive exenatide followed by insulin glargine (16 weeks each), or the reverse sequence of treatments, with all patients continuing their prestudy dose of metformin or sulfonylurea during the study.

The results from both treatment periods were identical with respect to glycem ic control: both treatments reduced HbA1c by about -1.4% in the completor population (exenatide, -1.43%; insulin glargine, -1.41%), and similar proportions of patients (40% and 41%, respectively) achieved an HbA1c level of 7.0% or less. The reduction of HbA1c observed during the first treatment period was maintained during the second treatment period regardless of the sequence. Irrespective of treatment sequence, however, weight decreased while patients were on exenatide (initial exenatide, -2.35 kg; period 2 exenatide, -2.3 kg), whereas weight increased when patients were receiving insulin glargine (initial insulin glargine, +0.75 kg; period 2 insulin glargine, +2.3 kg). These results again show the efficacy of GLP-1 agonists to improve glycem ia and induce weight loss in patients with T2DM.

Other GLP-1 agonists currently under development include a once-weekly, long-acting release (LAR) exenatide formulation, which has been shown to have good efficacy in glycemic control compared with placebo, as assessed by HbA1c levels, especially at the higher of the 2 doses tested. At week 15, the mean change from baseline in HbA1c was -1.4% and -1.7% for the
Incretin-based therapies, whether DPP-4 inhibitors or GLP-1 agonists, overcome many of the limitations associated with conventional therapies and may potentially improve markers of β-cell function and release. In particular, preclinical data for both classes of drugs suggest an expansion of β-cell mass. Whether these treatments can indeed alter the natural course of T2DM, and preserve or even restore β-cell function during disease progression remains to be seen with further long-term study.

**Conclusion**

Based on the availability of newer incretin therapies, clinicians can now design treatment regimens that go beyond simply targeting insulin deficits and insulin resistance associated with T2DM. There is now substantial evidence supporting the use of incretin-based therapies (both DPP-4 inhibitors and GLP-1 agonists) in combination with oral therapies, particularly with metformin, which may offer durable glycemic control in patients with T2DM while having a beneficial effect on weight (i.e., weight neutrality or weight loss). These agents also offer the advantages of improving glycemia and reducing HGP by suppressing glucagon produced by α cells.

Incretin-based therapies, whether DPP-4 inhibitors or GLP-1 agonists, overcome many of the limitations associated with conventional therapies and may potentially improve markers of β-cell function and release. In particular, preclinical data for both classes of drugs suggest an expansion of β-cell mass. Whether these treatments can indeed alter the natural course of T2DM, and preserve or even restore β-cell function during disease progression remains to be seen with further long-term study.

**References**


**Figure 6.** Comparison of incretin therapies for patients with type 2 diabetes mellitus. **Abbreviations:** DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1. **Source:** Drucker DJ. Diabetes Care. 2003;26(10):2929-2940.8

- 0.8-mg and 2.0-mg doses, compared to +0.4% in the placebo group (P<.001 for both exenatide LAR groups vs placebo) (Figure 5). The higher dose also resulted in significant weight reduction compared with placebo or the lower dose at 15 weeks of treatment; mean change from baseline in weight was -3.8 kg in the 2.0-mg group (P<.05 vs placebo) (Figure 5). Results of this study confirmed the efficacy in glycemic control and the benefit in weight loss of this convenient, once-weekly dosing formulation of exenatide.

- Gastrointestinal adverse events, particularly nausea and vomiting, are the most common side effects with GLP-1 agonists (Figure 6).9,31

- DPP-4 inhibitors or GLP-1 agonists, overcome many of the limitations associated with conventional therapies and may potentially improve markers of β-cell function and release. In particular, preclinical data for both classes of drugs suggest an expansion of β-cell mass. Whether these treatments can indeed alter the natural course of T2DM, and preserve or even restore β-cell function during disease progression remains to be seen with further long-term study.

- **References**

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