Therapy in the Early Stage: Incretins

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The complex pathological mechanisms responsible for development of type 2 diabetes are not fully addressed by conventional drugs, which are also associated with inconvenient side effects such as weight gain or hypoglycemia. Two types of incretin-based therapies are now in use: incretin mimetics (glucagon-like peptide-1 [GLP-1] receptor agonists that bind specific receptors and mimic the action of natural GLP-1) and incretin enhancers (inhibitors of the enzyme that degrade the incretin hormones and thus prolong their activity). Both offer important advantages over previous agents. In addition to the proven glucose-lowering efficacy, they promote weight loss (or are weight neutral) by slowing gastric emptying and inducing satiety, inhibit glucagon secretion with maintenance of counterregulatory mechanisms, and exhibit cardiovascular benefits, while having a low risk profile. Importantly, short-term studies have shown that incretins/incretin-based therapies protect β-cells (by enhancing cell proliferation and differentiation and inhibiting apoptosis) and stimulate their function (by recruiting β-cells to the secretory process and increasing insulin biosynthesis/secretion). These therapies have the opportunity to interfere with the disease progression if used as an early intervention, when enough β-cell mass/function can still be preserved or restored.

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PATHOPHYSIOLOGICAL CONSIDERATIONS—It has now become apparent that the pathophysiological defects leading to type 2 diabetes are much more complex than previously understood. Increased resistance to insulin action in the skeletal muscle and liver associated with enhanced hepatic glucose output and impaired insulin secretion due to a progressive decline of β-cell function are long-recognized core defects. But in addition, other mechanisms/organs are involved, augmenting the pathological pathways: adipocytes (altered fat metabolism due to insulin resistance), gastrointestinal tract (incretin deficiency and/or resistance), pancreatic α-cells (hyperglucagonemia and increased hepatic sensitivity to glucagon), kidneys (enhanced glucose reabsorption), and central nervous system (insulin resistance) (1). Chronic hyperglycemia and concomitant increase in free fatty acids and other lipid metabolites are associated with glucolipotoxicity, which further emphasizes insulin resistance and β-cell failure (by causing dedifferentiation of pancreatic β-cells, activation of stress response, accelerated apoptosis, and decreased proliferation) (2). The β-cell deficit with decreased secretory capacity is followed by a prevalent impairment of response to oral load (as compared with intravenous challenge); the combined β-cell dysfunction and incretin deficit is followed by hyperglycemia, which in turn further impairs incretin secretion and action by downregulating the receptors (2).

Ideally, all the above-mentioned pathogenic abnormalities should be addressed early by therapeutic strategies to obtain long-lasting glycemic control and delay disease progression. So far, therapeutic algorithms have been using oral agents in a stepwise fashion, adding them when specific glycemic targets are not met, but this approach (especially when sulfonylureas are used) does not prevent β-cell loss or assure durable glycemic control, and finally it leads to treatment failure (1). Moreover, the use of current agents is often hampered by their side effect profiles, mostly hypoglycemia, weight gain, or edema. Therefore, there has been a search for new agents that would address fundamental defects of type 2 diabetes and have minimal adverse effects.

INCRETINS—Incretins are gut-derived hormones, members of the glucagon superfamily, released in response to nutrient ingestion (mainly glucose and fat). They exert a wide range of effects, including stimulation of pancreatic insulin secretion in a glucose-dependent manner and play an important role in the local gastrointestinal and whole-body physiology (3).

Two gut hormones were found to mediate the "incretin effect" (that is, higher insulin release in response to an oral glucose challenge compared with an equal intravenous glucose load): glucose-dependent insulinotropic polypeptide (GIP) secreted from the L-cells of the distal ileum and colon and GLP-1 secreted from the K-cells in the duodenum and jejunum (4). The two hormones equally contribute to the incretin effect and have cumulative outcomes (5). GLP-1 release occurs biphasically, with an early phase (15–30 min) and a late phase (1–2 h); GIP has a similar secretion profile. The postprandial plasma levels increase approximately two- to threefold, with peak values depending on the meal size and content (5). It is believed that the early secretion (which accounts for most of the effect) is triggered by local nutrient-sensing pathways and neuronal and endocrine mediators, while the late-phase release is produced by a direct nutrient contact (3–5). After secretion, incretins are rapidly degraded due to the action of dipeptidyl peptidase-4 (DPP-4), an ubiquitous enzyme found on the surface of epithelial and endothelial cells but also found in plasma (6). The GLP-1 half-life is <2 min, whereas that of GIP is ~5–7 min, and both are rapidly cleared by the kidneys (5).

The incretins act by binding to their specific G-protein–coupled receptors: the GIP receptor is found in pancreatic β-cells, adipose tissue, and the central nervous system, whereas the GLP-1 receptor (GLP-1R) is expressed in islet α- and β-cells,

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gastrointestinal tract, the central nervous system, heart, lung, and kidney (5,7). Engagement of the GLP-1Rs activates adenylate cyclase, induces production of AMP and the downstream pathways, and finalizes with various biological actions, such as insulin synthesis and secretion.

BIOLOGICAL EFFECTS OF INCRETINS/INCRETIN-BASED THERAPIES

Pancreatic effects

GLP-1 and GLP-1R agonists have pleiotropic actions at the pancreatic level. After binding to specific receptors on β-cells, they promote insulin gene transcription and its biosynthesis and stimulate insulin secretion in a glucose-dependent manner (8,9). Because stimulation of (pro)insulin synthesis occurs at the translational level, β-cell secretory capacity and insulin stores are maintained (8,10). GLP-1 and GLP-1R agonists shift the dynamics of insulin secretion toward an earlier response and restore the biphasic profile (11,12). In addition, there is an upregulation of biosynthesis of other β-cell products such as glucokinase and glucose transporters (GLUT2), which improves the capacity of β-cells to sense and respond to glucose (13).

It has also been shown that GLP-1R activation stimulates the differentiation of islet precursor cells into insulin-producing cells and promotes β-cell proliferation/neogenesis, while enhancing resistance to apoptosis (14,15). The net result is promotion of cell survival and an increase in β-cell number. Pancreatic β-cell mass preservation may be obtained through a direct action on β-cells (by modulating proliferation, neogenesis, and apoptosis) and/or an indirect one (by reducing the circulating levels of glucose and free fatty acids and, in consequence, glucolipotoxicity) (5). However, it should be mentioned that these effects have been proven mainly by short-term studies, and whether chronic therapy with GLP-1R agonists or DPP-4 inhibitors is followed by sustained improvements in β-cell mass/function needs to be further demonstrated. The GIP actions on islet β-cells are similar to those exhibited by GLP-1.

GLP-1 also modulates the function of α-cells as it inhibits glucagon secretion in a glucose-dependent way. The capacity to release glucagon when blood glucose levels are low is preserved; hence, the normal counterregulatory mechanisms are not affected, even at high GLP-1 concentrations (16). Some data suggest that GLP-1 participates in the fine-tuning of glucose homeostasis also through stimulating somatostatin secretion by δ-cells, which inhibit glucagon and insulin release (17).

Extrapancreatic effects

As GLP-1Rs are abundant in many tissues other than the pancreas, their activation is associated with a broad variety of extrapancreatic effects, some contributing to the glucoregulatory actions.

Gastrointestinal system. The incretin hormone GLP-1 and GLP-1R agonists exert inhibitory actions on meal-stimulated gastric acid secretion and on gastric emptying in a dose-dependent fashion. The deceleration of gastric emptying is associated with blunting of postprandial glucose excursions and insulin levels, thus having an important impact on glucose control (18). The mechanisms implicated in the effects on gastrointestinal system are complex and not fully elucidated: it has been proposed that a direct action on GLP-1R expressed on gastric parietal cells may be involved and/or that indirect vagal-mediated neural actions may be responsible (5). Some authors suggested that GLP-1 participates in a negative-feedback gastrointestinal loop in which proximal events are inhibited by nutrients that stimulate GLP-1R activity in the distal parts of small intestine (19).

Central and peripheral nervous system. Experimental and clinical data demonstrate that GLP-1 and GLP-1R agonists regulate feeding behavior by enhancing satiety/suppressing appetite and inhibiting caloric intake, which results in weight loss (5). It is believed that the mechanisms of action are direct ones, since the GLP-1 and GLP-1R agonist are small molecules that can diffuse across the blood-brain barrier and activate the widespread GLP-1Rs found throughout the brain (particularly in hypothalamus nuclei). Alternatively, there could be indirect mechanisms via neural (vagal) pathways and/or through inhibition of gastric emptying, which induces gastric distension and sensation of fullness (5,7).

Studies imply that GLP-1 and GLP-1 agonists might also have antiapoptotic, proliferative, and neuroprotective actions of peripheral and central nervous systems; reduce neurofunctional deficits; and improve learning and memory (20,21).

Cardiovascular system. Data coming mainly from animal studies indicate that both GLP-1 and GLP-1R agonists/DPP-4 inhibitors have cardioprotective effects (mediated directly via GLP-1Rs as well as indirectly by GLP1 metabolites [GLP-1 9–36 NH_2] in the myocardium). GLP-1 attenuates myocardial stunning, reduces infarct size, and improves regional wall motion at the infarct site and myocardial glucose uptake; left ventricular function and cardiac output, as well as systemic vascular resistance, are ameliorated (22,23). Protective effects against myocardial ischemia-reperfusion injury, reduction of infarct size, and improvement of cardiac function have been demonstrated for GLP-1R agonists and DPP-4 inhibitors in both animal models and humans (24–27).

In addition, GLP-1 improves endothelial function and attenuates atherosclerotic lesions by reducing monocyte/macrophage accumulation in the arterial wall (28). The effects on blood pressure are not so clear: some studies report no significant changes, whereas others indicate a small decrease of systolic and diastolic blood pressure levels (29). The antihypertensive and the cardiac/renoprotective effects (reduction in albuminuria, proteinuria, and glomerular injury) might be due to an increase in water and sodium urinary excretion and a reduction of glomerular hyperfiltration (30,31).

Lipid metabolism. The effects of GLP-1 and incretin-based therapies (GLP-1R agonists/DPP-4 inhibitors) on lipid metabolism are either neutral or slightly beneficial, with a minimal decrease of fasting LDL cholesterol and triglycerides and a small increase of HDL cholesterol (32). Long-term studies have shown that the improvement of fasting lipid profile is more evident and parallels the body weight loss (33). In contrast, the GLP-1 and GLP-1 agonists seem to significantly reduce postprandial lipid levels (triglycerides, free fatty acids), possibly because of the gastric emptying delay and/or improved insulin-mediated inhibition of lipolysis (34,35).

Insulin-sensitive tissues (liver, muscle, and adipose tissue). There is a tight metabolic interaction between the liver and the intestine, mediated in part by the portal vein, and incretins seem to play a role in influencing hepatic metabolism (36). In animal models, GLP-1 inhibits hepatic glucose output (associated with reduced expression of hepatic enzymes involved in gluconeogenesis and glycogenolysis) and augments incorporation of glucose into glycogen (37). The mechanism by which GLP-1 regulates the hepatic glucose output appears to be related to the modulation of the hepatic insulin receptor–GLUT2 complex endocytosis

(7). In addition, GLP-1 improves hepatic insulin sensitivity by restoration of insulin signaling, since basal levels of insulin receptor substrate-1 are enhanced (5,37). In vitro studies have demonstrated that human hepatocytes express GLP-1R and that GLP-1R agonists activate pathways downstream of insulin receptor substrate-2 and decrease triglyceride content from steatotic hepatocytes (38). Evidence from animal studies also indicates that treatment with GLP-1R agonists is associated with reversal of hepatic steatosis, whereas in humans, it improves hepatic biomarkers (33,39). Data regarding the effects on muscle and adipose tissue is sparse and mainly comes from in vitro and animal studies. Apparently, GLP-1 and GLP-1R agonists stimulate glucose uptake and glycogenogenesis in muscle, while in adipocytes, GLP-1R agonists increase insulin-stimulated glucose uptake and GLP-1 has lipolytic effects (5,40). Taken together, these results imply that the incretins might improve insulin sensitivity, even if this effect is not preponderant among all their biological actions.

Other tissues. Some preliminary data described additional favorable actions at various levels, such as the hypothalamic-pituitary neuroendocrine axis, respiratory tract, and bone metabolism, but they need further confirmation (5,32).

CLINICAL DATA IN TYPE 2 DIABETES: EFFICACY AND SAFETY

—The clinical use of incretins in their native forms has been hampered by the fact that they have a short half-life because of a rapid inactivation by DPP-4, and a continuous infusion is impractical. Hence, the new therapeutic agents that have been developed to exploit the biological potential of incretins are basically using two different approaches: one uses GLP-1R agonists (degradation-resistant synthetic/chemically modified peptides) that bind GLP-1Rs and mimic the action of naturally occurring GLP-1 (incretin mimetics) and the other inhibits DPP-4 and thus prolongs the activity of endogenous incretin hormones by diminishing their degradation (incretin enhancers) (41).

Several incretin-based therapeutic agents are already on the market or under development: exenatide, liraglutide, and exenatide long-acting release (LAR); taspoglutide and albiglutide (GLP-1 agonists); and sitagliptin, vildagliptin, saxagliptin, and alogliptin (DPP-4 inhibitors) (Table 1) (45).

A number of trials have evaluated the efficacy and safety of incretin-based therapies in subjects with type 2 diabetes and demonstrated positive results in terms of glycemic control and other clinical or biological parameters that are briefly reviewed here.

GLP-1R agonists

Glycemic outcomes. Measures of glycemic efficacy have been assessed in clinical trials that had different designs (treatment duration, patient population, etc.) that preclude a direct head-to-head comparison of the potencies of the drugs. When used as monotherapy, all GLP-1 agonists significantly decreased mean HbA_{1c} levels compared with placebo: with 0.7/0.9% for 5 μg/10 μg twice-daily exenatide ($P = 0.003/P < 0.001$; 24-week trial), with 1.4/1.7% for 0.8 mg/2.0 mg exenatide LAR ($P < 0.0001$ for both doses; 15-week study), and with 1.74/1.69% for 1.9 mg/1.25 mg liraglutide ($P < 0.0001$ for both doses; 14-week trial) (46,47). In comparison with a sulfonylurea (glimepiride), 1.2 mg/1.8 mg liraglutide significantly reduced the mean HbA_{1c} level by 0.84/1.14% ($P < 0.01/P < 0.001$, respectively) in a 52-week trial (47,48).

Combination therapies have basically yielded similar HbA_{1c} reductions. In association with metformin, twice-daily exenatide decreased mean HbA_{1c} level by 0.4/0.8% (5 μg/10 μg, respectively; $P < 0.002$ vs. placebo for both doses; 30-week trial) and liraglutide by 0.7/1.0/1.0% (0.6 mg/1.2 mg/1.8 mg, respectively; $P < 0.0001$ vs. placebo for all doses; 26-week trial). In combination with a sulfonylurea, mean HbA_{1c} was lowered by 0.5/0.9% for 5 μg/10 μg exenatide b.i.d., respectively ($P < 0.001$ for both doses; 30-week study) and by 0.6/1.1/1.1% for 0.6 mg/1.2 mg/1.8 mg of liraglutide, respectively ($P < 0.0001$ vs. placebo for all doses; 26-week trial). Mean HbA_{1c} was reduced by 0.9% when 10 μg exenatide b.i.d. was added to a thiazolidinedione ($P < 0.001$) in a 16-week trial (46,47). Similar results were obtained when GLP-1R agonists were used in triple therapy (with a thiazolidinedione plus metformin or sulfonylurea plus metformin) (47).

A meta-analysis that combined data from randomized control trials using a GLP-1R agonist (with at least 12 weeks' duration) indicated a significant decline of HbA_{1c} from baseline compared with placebo (weighted mean difference −0.97%; 95% CI −1.13 to −0.81) (48). Moreover, a higher proportion of patients treated with a GLP-1R agonist reached target goals of HbA_{1c} <7.0% compared with placebo/standard treatment groups at the end of the study periods (49,50).

Fasting glucose levels significantly decreased with GLP-1R agonists both in monotherapy or when combined with other drugs, and studies also reported significant improvements in postprandial blood glucose concentrations (47–50).

Nonglycemic outcomes. Treatment with GLP-1R agonists in monotherapy or in combination has been associated with a substantial, progressive, sustained, and dose-dependent decrease in body weight (46,47,49). The weight loss was significantly

Table 1—*Overview of approved incretin-based therapies (42–44)*

Drug (trade name)	Dose/frequency of dosing	Route of delivery	Pharmacokinetics ($T_{max}/T_{1/2}$)	Approved indications
GLP-1R agonists				
Exenatide (Byetta)	5 μg, 10 μg b.i.d.	SC	2.1 h/2.4 h	Monotherapy*/combination therapy
Liraglutide (Victoza)	0.6 mg, 1.2 mg, 1.8 mg q.d.	SC	8–12 h/~13 h	Combination therapy
DPP-4 inhibitors				
Sitagliptin (Januvia)	100 mg q.d.	PO	1–4 h/12.4 h	Monotherapy/combination therapy
Vildagliptin† (Galvus)	100 mg b.i.d. (50 mg q.d.‡)	PO	1.7–2.5 h/3 h	Combination therapy
Saxagliptin (Onglyza)	2.5 mg§, 5 mg q.d.	PO	2 h/2.5 h	Monotherapy*/combination therapy

SC, subcutaneously; PO, orally. *Approved by the U.S. Food and Drug Administration (FDA) only. †Approved by European Medicines Agency (EMA) only. ‡When associated with a sulfonylurea. §Recommended by the FDA.

greater versus comparator groups (weighted mean difference −2.37 kg; 95% CI −3.95 to −0.78) (48). Both exenatide and liraglutide significantly improved β-cell function as assessed by homeostasis model assessment (HOMA-B) (ranging from 19 to 70% for exenatide and 20 to 44% for liraglutide) or by the proinsulin-to-insulin ratio (41,43,44). A head-to-head comparison of the two agents showed a significantly greater improvement of HOMA-B with liraglutide (32.1 vs. 2.7% with exenatide) (47).

Additional positive effects were noted with GLP-1R agonists in terms of improvement in hepatic injury markers (aminotransferases significantly decreased with long-term exenatide treatment compared with baseline in subjects with increased levels at the start; $P < 0.001$), in blood pressure (small but significant reductions; up to 6.7 mmHg, mostly for systolic values, both with exenatide and liraglutide), and in lipid profile (some studies reported an increase in HDL cholesterol and reduction in triglycerides and LDL cholesterol with exenatide) (47–50). Whether the positive impact on cardiovascular risk factors actually translates into improvement of cardiovascular disease and mortality remains to be demonstrated in outcome studies.

Adverse events. The most frequently reported side effect was nausea both with exenatide (3–51%) and liraglutide (5.2–40.0%) therapy (48,49). The severity was mild to moderate, and the incidence decreased after 3–4 weeks (liraglutide) and ~8 weeks (exenatide) of treatment. A smaller proportion of patients also experienced vomiting.

There was a low risk of hypoglycemia in clinical trials, and severe hypoglycemia occurred rarely with both drugs (this happened mainly when associated with a sulfonylurea) (47–49). Development of antiliraglutide autoantibodies occurred at relatively low rates, whereas higher frequencies were noticed for anti-exenatide autoantibodies. However, they did not affect outcomes and were not associated with adverse events (48,49).

A recent literature review (including the U.S. Food and Drug Administration data) evaluated the possible association between GLP-1 agonist use and the risk of pancreatitis. Up-to-date observational reports and clinical study data revealed that 44 cases of acute pancreatitis occurred in patients with type 2 diabetes while taking exenatide (8 cases during clinical development and 36 postmarketing reports), 4 cases of pancreatitis in liraglutide-treated patients (in clinical trials), and none during therapy with albiglutide or taspoglutide (51). However, a clear causal association with GLP-1 agonist therapy could not be established, since most of the patients had additional risk factors for pancreatitis and because type 2 diabetes itself seems to increase the risk for developing pancreatitis independent of drug therapy (51). Nevertheless, the prescribing information for exenatide and liraglutide recommends that the drugs should be discontinued if pancreatitis is suspected and should not be restarted if pancreatitis is confirmed.

Because the GLP-1R agonists have not been used long term in humans, the potential side effects of long-term administration of pharmacologic concentrations should be evaluated.

DPP-4 inhibitors

Glycemic outcomes. Monotherapy with 100 mg/200 mg sitagliptin significantly lowered mean HbA_{1c} levels compared with placebo by 0.61/0.76% ($P < 0.001$ for both doses) in a 24-week trial and by 0.48/0.36% ($P < 0.001$ for both doses) in an 18-week study, whereas mean HbA_{1c} level was decreased by 0.8/0.9% with 50 mg/100 mg vildagliptin, respectively, after a 24-week intervention ($P = 0.006$/$P < 0.001$) (46,47,52). A low-dose (2.5, 5, 10, 20, or 40 mg) intervention with saxagliptin for 12 weeks reduced HbA_{1c} levels by 0.7–0.9% compared with placebo in all treatment arms, and a high-dose (100 mg) 6-week intervention decreased HbA_{1c} levels by 1% (44). When compared with metformin, vildagliptin in monotherapy significantly reduced mean HbA_{1c} from baseline by 1.0% (100 mg, $P < 0.001$; 52-week trial), but statistical noninferiority of vildagliptin 50 mg b.i.d. to metformin 1,000 mg b.i.d. was not demonstrated (53).

In combination with metformin, vildagliptin reduced mean HbA_{1c} by 0.7% (100 mg, $P < 0.0001$; 24-week trial) and sitagliptin by 0.5/0.9% compared with placebo (50 mg/100 mg, $P < 0.001$; 24-week trial), while with 2.5 mg/5 mg/10 mg saxagliptin, the mean placebo-subtracted HbA_{1c} was 0.73/0.83/0.72%, respectively ($P < 0.0001$ for all doses; 24-week treatment) (44,46). In association with a sulfonylurea, 100 mg sitagliptin decreased HbA_{1c} by 0.4% compared with placebo ($P < 0.001$) in a 24-week study and 50 mg/100 mg vildagliptin by 0.6% ($P < 0.001$, for both doses; 24-week trial). In combination with a thiazolidinedione, HbA_{1c} was lowered by 0.8% after the 24-week therapy with 100 mg sitagliptin ($P < 0.001$), by 0.8/1.0% with 50 mg/100 mg vildagliptin ($P < 0.001$), and by 0.66/0.94% with 2.5 mg/5 mg saxagliptin ($P = 0.0007$/$P < 0.0001$) (46,54). A similar decrease (0.45%) was noticed in a 24-week trial in combination with two other oral agents (metformin plus sulfonylurea) compared with placebo (47).

A meta-analysis of data from randomized control trials longer than 12 weeks with DPP-4 inhibitors showed significantly lower HbA_{1c} compared with placebo (weighted mean difference −0.74%; 95% CI −0.85 to −0.62); additionally, patients receiving a DPP-4 inhibitor were more likely to achieve HbA_{1c} levels of <7.0% compared with placebo (48).

Clinical studies have also shown reductions of fasting glucose concentrations with all three DPP-4 inhibitors versus placebo in monotherapy or associated with other oral agents (with a sulfonylurea, the effects were modest), as well as reductions of postprandial glycemia (46,48).

Nonglycemic outcomes. Studies that reported weight changes with DPP-4 inhibitors have found either small decreases or increases (the highest weight gain occurring in combination with thiazolidinediones); in general, they are considered weight neutral. Sitagliptin, saxagliptin, and vildagliptin have all improved β-cell function evaluated by HOMA-B and proinsulin-to-insulin ratios (47,55,56). Some improvements in HDL and LDL cholesterol and triglycerides have been reported in some studies, whereas others indicated no significant effects (48). Long-term studies with cardiovascular end points are needed to evaluate the effect of incretin enhancers on cardiovascular morbidity and mortality.

Adverse events. In clinical studies, all DPP-4 inhibitors were well tolerated with low rates of side effects. Mild-to-moderate hypoglycemia occurred at a low frequency, and there was practically no difference between DPP-4 inhibitors and comparator groups (48). Among other side effects, headache, urinary tract infections, and nasopharyngitis appeared to be more frequent, whereas gastrointestinal adverse effects occurred rarely (47,48).

DPP-4 inhibitors not only act by enhancing the activity of incretins, but they cleave other substrates, such as neuropeptides, gastrointestinal hormones, cytokines, or chemokines and also have an effect on immunomodulation, cell adhesion, and cell movement. These pleiotropic effects

have raised some concerns regarding the long-term safety of their use. Although, in clinical studies and in clinical use so far they have not demonstrated major adverse effects, the consequences of long-term therapy with DPP-4 inhibitors (especially in susceptible patients with other chronic diseases) need to be evaluated.

GLP-1R agonists versus DPP-4 inhibitors. Apart from their different mechanisms of action, there are other elements that distinguish these two classes of drugs, which can help clinicians identify patients who would most likely benefit from the therapeutic intervention with either of them.

First is the route of administration: GLP-1R agonists require subcutaneous administration, whereas DPP-4 inhibitors are delivered as oral tablets, and this difference might be significant in terms of convenience of use and adherence to therapy.

Second is the influence on body weight: GLP-1R agonists cause significant and sustained weight loss, whereas DPP-4 inhibitors are rather weight neutral, so obese subjects are more likely to benefit from therapy with a GLP-1R agonist.

Third is the occurrence of side effects: therapy with GLP-1R agonists is associated with a higher incidence of adverse gastrointestinal effects, particularly nausea, whereas with DPP-4 inhibitors, infections seem to be more frequent.

These are the most obvious differences, but some other considerations should be made. GLP-1R agonists are generally seen as having a more robust glucose-lowering efficacy, since the mean HbA_{1c} reductions are somewhat more pronounced (~0.5–1% with DPP-4 inhibitors and ~0.6–1.5% with GLP-1R agonists) (57). A recent parallel-group study comparing liraglutide with sitagliptin as add-on therapy to metformin supported this assumption, demonstrating greater lowering of mean HbA_{1c} with liraglutide than with sitagliptin (mean treatment differences for 1.8 mg/1.2 mg liraglutide vs. 100 mg sitagliptin were −0.60/−0.34%, $P < 0.0001$) (58). It should also be noted that a head-to-head crossover study comparing exenatide with sitagliptin has shown that, while both agents lowered the 2-h postprandial glucose levels, the overall reduction was greater with exenatide and, at the end of trial, the values were in the normal range (whereas for sitagliptin, they were still in the hyperglycemic range) (59). In addition, exenatide significantly reduced postprandial glucagon compared with sitagliptin and slowed gastric emptying (58). These are important findings that need consideration (especially the effect on postprandial glycemic concentrations), since they might have significant clinical implications. Certainly, further confirmations from long-term trials are desirable.

The differences observed between incretin mimetics and incretin enhancers might be in part explained by higher pharmacological circulating levels of GLP-1R agonists and possibly stronger receptor stimulation compared with physiological concentrations of endogenous GLP-1 achieved after DPP-4 inhibition.

INCRETIN-BASED THERAPY IN THE PREDIABETIC STAGE

—Subjects with abnormal glucose tolerance seem to have an impairment in incretin hormone secretion/activity. However, data coming from the few studies that have evaluated these subjects in this population are not consistent. One study reported reduction of GLP-1 levels (but not GIP) in subjects with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT); another indicated decreased levels of GIP in IGT and increased levels of GLP-1 in IFG during an oral glucose tolerance test; and a third study showed that the GIP response to oral glucose is impaired in women with IGT, whereas GLP-1 response is not affected (60–62). Some of this controversy may be due to the selection of the patient group, because confounding factors, such as obesity and impaired gastric emptying, also appear to be associated with decreased GLP-1 levels. Insulin resistance at the level of the intestinal L-cell can impair secretagogue-induced release of GLP-1, whereas reduced insulin sensitivity in normal individuals is linked to lower levels of GLP-1 (63,64). Finally, regardless of actual circulating GLP-1 levels, several studies have identified a polymorphism in the gene for *TCF7L2* as a major risk factor for type 2 diabetes that is also associated with an impaired ability of GLP-1, as well as of GIP, to stimulate insulin secretion (65). Therefore, observational studies that follow prospectively the changes of incretin hormones from normal glucose status to overt type 2 diabetes are needed to elucidate the natural history of incretin alterations.

There is limited evidence regarding the efficacy of incretin-based therapy in the prediabetic population. Although, some preliminary data suggest that obese subjects with IFG or IGT receiving exenatide along with lifestyle intervention for 24 weeks reverted to normal glucose tolerance at the end point (77% exenatide vs. 56% placebo) (66).

Improvement in postprandial glycemia was shown in individuals with IFG treated with vildagliptin for 6 weeks, but the effect was not sustained after washout, possibly because of the short treatment duration (67). A 12-week study, however, in individuals with IGT treated with vildagliptin reported reduction of peak glycemic excursions and incremental glucose AUC with a concomitant increase of postprandial GLP-1 levels (68). In contrast, sitagliptin did not alter fasting or postprandial glucose concentrations in subjects with IFG after 8 weeks of treatment, but again, it is not clear if the duration of therapy was sufficient for the effects to come about (69).

So incretin-based therapy of longer duration appears to bring some beneficial effects in the prediabetic stage, and it could be used as an intervention to prevent or delay progression to overt type 2 diabetes. However, at the moment, this is just a speculative assertion, and before long-term and large prevention trials are conducted to evaluate this potential, it should be determined unequivocally that incretin-based therapies improve glucose homeostasis (and maybe also β-cell function/mass) in prediabetic individuals.

WHY SHOULD WE USE INCRETIN-BASED THERAPIES IN EARLY STAGES OF TYPE 2 DIABETES?

—Given the increased knowledge regarding the natural history of type 2 diabetes, an approach that addressed the pathophysiological features leading to disease progression and not only the prevention of glycemic deterioration is desirable. Currently, available therapies are associated with some drawbacks such as weight gain, risk of hypoglycemia, efficacy, or convenience, ultimately resulting in suboptimal long-term glycemic control. This result is in part because most therapeutic agents do not directly target or protect β-cell mass, which is essential for the economy of disease, considering that the progression of type 2 diabetes parallels the wane of β-cell function (70). Thus, an intervention that better preserves β-cell function and mass might have a better chance of obtaining and maintaining good metabolic control long term (1).

The new incretin-based therapies offer appealing advantages over existing

drugs, and there are several reasons for recommending them. Aside from glucose-dependent insulin stimulation and a proven glucose-lowering efficacy, they have other concomitant beneficial effects, such as low risk of hypoglycemia, inhibition of the glucagon secretion with maintenance of counterregulatory mechanisms, promotion of weight loss (or a weight-neutral effect), and possible cardiovascular benefits (improvement of lipid profile, blood pressure, endothelial, and myocardial function). The positive impact on cardiovascular risk factors is certainly advantageous for individuals with diabetes that often is associated with hypertension, dyslipidemia, and obesity. Therefore, there is potential to decrease cardiovascular morbidity and mortality associated with type 2 diabetes, but this should be confirmed by long-term clinical studies.

Even more relevant are the effects on islet β-cells. At least in the short term, incretin-based therapies stimulate β-cell proliferation and differentiation, recruit more β-cells to the secretory process, increase insulin biosynthesis, improve insulin content, and have antiapoptotic effects. Certainly, studies need to demonstrate sustained long-term effects, but considering the progressive decline in β-cell number and function over time, a therapeutic approach that interferes with this process has the potential to slow down disease progression. In fact, incretin-based therapies and thiazolidinediones are the only available antidiabetic agents that have been shown to exert protective effects on β-cell function (1). It is easy to envisage that the earlier one would use such an intervention, greater β-cell mass/function is preserved (or maybe even enhanced) and better long-term outcome of the disease. The chances of beneficial β-cell salvage are higher in an early phase because the threshold for reversibility has not yet been surpassed.

In conclusion, incretin-based therapy is a valuable add-on to the therapeutic spectrum for type 2 diabetes that offers the possibility of targeting many pathophysiological abnormalities associated with the disease. Incretins might even be disease-modifying agents that have the potential to delay the onset or slow the progression of diabetes, but this needs to be proven by clinical trials.

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