Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects

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Incretin-based therapies encompass two new classes of antidiabetic drugs: glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, and exenatide long-acting release), which are structurally related to GLP-1, and the dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin and saxagliptin), which limit the breakdown of endogenous GLP-1. To evaluate the safety and effectiveness of incretin-based therapies for the treatment of type 2 diabetes mellitus and the role of these therapies in clinical practice, a MEDLINE search (January 1985–November 2009) was conducted. Relevant references from the publications identified were also reviewed. Of 28 studies identified, 22 were randomized controlled trials. Data show that these therapies affect insulin secretion in a glucose-dependent manner, achieving clinically meaningful reductions in hemoglobin A_{1c} levels, with very low rates of hypoglycemia. In addition, reductions in body weight have been observed with GLP-1 receptor agonists, which also exert a pronounced effect on systolic blood pressure. Various human and animal studies show that GLP-1 improves β-cell function and increases β-cell proliferation in vitro, which may slow disease progression. Thus, incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes.

Key Words: type 2 diabetes, incretin-based therapies, glucagon-like peptide-1, GLP-1, dipeptidyl peptidase-4, DPP-4.

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The increasing prevalence of diabetes mellitus is an acknowledged world health crisis that is both a major contributor to patient morbidity and mortality and a huge economic burden.[1] The complex pathophysiology of type 2 diabetes makes effective treatment problematic. Hyperglycemia is associated with an increased risk of microvascular complications, sensory neuropathy, myocardial infarction, stroke, macrovascular mortality, and all-cause mortality.[2] Type 2 diabetes is also linked causally with obesity—in itself a global health crisis—which independently increases the risk of serious cardiovascular comorbidities.[1] Hypertension, also often associated with type 2 diabetes, can further increase cardiovascular risk.

The global economic impact of diabetes, due to premature death and complications from the disease, is considerable. At least $232 billion were spent on treatment and prevention of diabetes worldwide in 2007, with three quarters of that

amount spent in industrialized countries on the treatment of long-term complications and on general care, such as efforts to prevent micro- and macrovascular complications.[3] The indirect costs of the disease must also be included in any discussion of its burden. In 2007, it was estimated that disability, lost productivity, and premature death due to diabetes cost the United States economy alone $58 billion.[1]

Treatment Potential for Type 2 Diabetes Mellitus

Insulin resistance and impaired insulin secretion both contribute to the development of type 2 diabetes, with the shift from normal to impaired glucose tolerance and then to diabetes, accompanied by a 40% decrease in insulin sensitivity and a 3–4-fold deterioration in insulin secretion due to loss of β-cell capacity (50–80%).[4, 5] However, if impaired glucose tolerance is diagnosed early enough, overt type 2 diabetes can be prevented or at least delayed, with lifestyle interventions aimed at reducing calorie intake and body fat[6, 7] or through drug treatment[7] to normalize glycemic control. Once type 2 diabetes has been diagnosed, weight loss alone can greatly improve both glycemic control and patients' cardiovascular risk profiles.[8] The effects are interrelated: glycemic control, coupled with effective management of additional risk factors, benefits cardiovascular prognosis.[9]

Despite treatment guidelines that recommend early, aggressive intervention,[10, 11] many patients fail to reach targets for glycemic control (~43% of patients in the United States have hemoglobin A_{1c} [A1C] levels ≥ 7%),[12] with minority groups having greater disease prevalence.[13, 14]

Many factors contribute to the failure to manage type 2 diabetes successfully. The most fundamental of these are the necessary lifestyle modifications, which, if not implemented at the time of diagnosis, may result in further decline in glycemic control and hasten the need for pharmacotherapy. Other factors include psychosocial and economic influences and shortcomings in the efficacy and tolerability profiles of many available antidiabetic drugs.

Goals of Therapy and Limitations of Current Treatments

To successfully improve patient outcomes and minimize the risk of complications and their cost, treatment should ideally address deteriorating β-cell function, A1C, and fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels simultaneously, without increasing risk of hypoglycemia, weight gain, or cardiovascular disease contributors. Adequate glycemic control is essential, as reduction of A1C levels can decrease the risks of microvascular and macrovascular complications and mortality associated with type 2 diabetes.[2] For every 1% reduction in A1C, a 37% decrease in risk for microvascular complications ($p<0.0001$) and a 21% decrease in risk of death related to diabetes ($p<0.0001$) have been observed.[2] An ideal treatment would reduce cardiovascular risk factors as well as control blood glucose levels.

Current guidelines for type 2 diabetes from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocate a stepwise escalation of intervention, starting with lifestyle modification and metformin[15]; however, sulfonylureas, a common second-line intervention in type 2 diabetes treatment regimens, are limited by a failure of β-cell function that underlies the progression of the disease. Although β-cell function cannot be measured directly in humans, several indicators can be used to monitor its decline. These include the homeostatic model assessment of β-cell function (HOMA-B), which yields an estimate from fasting plasma insulin and glucose concentrations,[16] and the proinsulin:insulin ratio. The HOMA-B results have shown that established oral antidiabetic drug therapies such as metformin, sulfonylureas, and thiazolidinediones can improve β-cell function during the first year of treatment when they are given as initial treatment in patients with newly diagnosed type 2 diabetes; however, β-cell function declines progressively thereafter.[4, 17, 18] The A1C level parallels these changes in β-cell function, decreasing in the first year of therapy and then increasing progressively, highlighting the need for therapies that can sustain improvements in β-cell function.[19]

Insulin therapy is necessary once β-cell secretory capacity becomes insufficient; however, alternative antihyperglycemic drugs—the incretin-based therapies—are now available that may offer advantages over conventional oral antidiabetic drug therapies. These incretin-based agents were included in the 2009 recommendations of an American Association of Clinical Endocrinologists–American College of Endocrinology consensus panel,[20] which suggested that patients with A1C levels of 7.6–9.0% be treated with dual therapy with metformin

(unless contraindicated) plus, in order of preference, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, glinides, or sulfonylureas. The panel emphasized the lower risk of hypoglycemia with GLP-1 receptor agonists and DPP-4 inhibitors compared with glinides and sulfonylureas, but preferred GLP-1 receptor agonists over DPP-4 inhibitors because of their greater potential for lower PPG level and substantial weight loss. For patients requiring triple therapy, metformin, a GLP-1 receptor agonist, and a third oral antidiabetic drug—a thiazolidinedione, a sulfonylurea, or a glinide—are recommended.

Incretin-Based Therapies

Physiologic Effects of Glucagon-Like Peptide-1

The "incretin effect" describes the phenomenon whereby a glucose load delivered orally produces a much greater insulin secretion than the same glucose load administered intravenously.[21] This effect is mediated by two incretin hormones secreted by intestinal cells.[22] Glucose-dependent insulinotropic polypeptide (GIP) was identified first,[22] followed by GLP-1.[23] It is now thought that healthy individuals may derive up to 70% of their prandial insulin secretory response from the incretin effect.[24] Under normal conditions, the incretin peptides are secreted as needed, in response to ingested nutrients, and have a short plasma half-life due to degradation by the ubiquitous DPP-4 enzyme.[25]

In people with type 2 diabetes, pancreatic responsiveness to GLP-1 is impaired,[26] but the insulin-secretory response can be restored with pharmacologic doses of human GLP-1.[27] Further studies in vitro and in animals show that GLP-1 promotes β-cell neogenesis and preservation[28–30] and inhibits β-cell apoptosis.[30, 31] Also, GLP-1 has potentially beneficial effects on cardiac function: it has been shown to be cardioprotective in ischemia-reperfusion models in rats in vivo,[32] and to reduce blood pressure in Dahl salt-sensitive rats.[33] In humans, GLP-1 improves left ventricular function as well as endothelial function in patients with high cardiac risk.[34, 35] Along with these benefits, GLP-1 has been shown to slow the rate of gastric emptying in humans[36] and to reduce appetite.[37] These effects are particularly important, since type 2 diabetes is often associated with obesity and excessive caloric intake. It is clear that drugs acting through the physiologic GLP-1 pathways might have important ancillary benefits for the treatment of type 2 diabetes.

A key feature of GLP-1 action is the glucose-dependent stimulation of insulin secretion and concomitant suppression of glucagon. When patients with type 2 diabetes are infused with human GLP-1, insulin levels return toward basal levels when normal FPG concentrations are reached, despite ongoing infusion of GLP-1.[38] Continuous subcutaneous GLP-1 infusion for 6 weeks also reduced A1C by 1.3% and FPG by 77 mg/dl, slowed gastric emptying, and reduced appetite and body weight by 1.9 kg.[39] Therefore, GLP-1 and therapies that activate GLP-1 receptors only stimulate increases in insulin secretion when glucose levels are elevated and, as a result, carry a very low risk of hypoglycemia (Figure 1) unless combined with a sulfonylurea or insulin.

Unfortunately, therapeutic use of human GLP-1 is not practical due to its rapid degradation by DPP-4 enzyme,[25] with an elimination half-life of

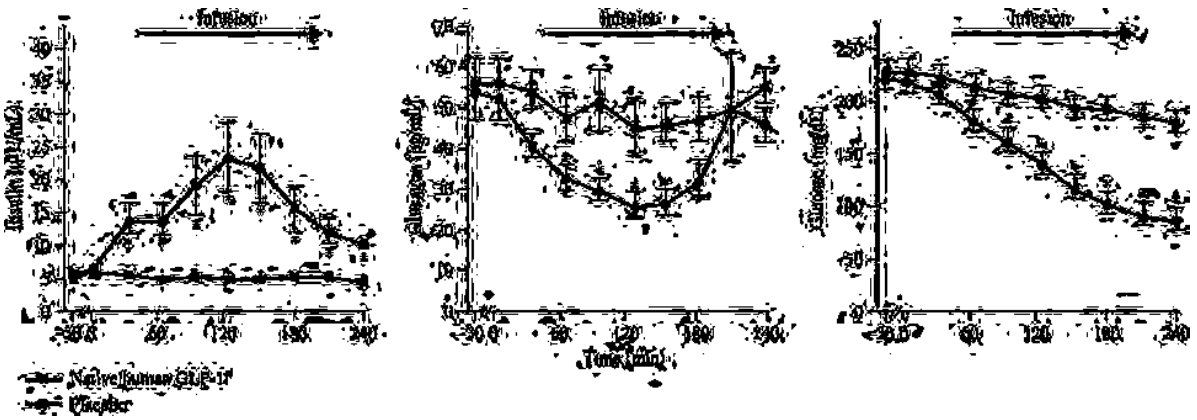

Figure 1. Effects of glucagon-like peptide-1 (GLP-1) or placebo infusion on insulin, glucagon, and glucose levels. *p<0.05. (From reference 38 with permission.)

about 2 minutes.[27] As a result, two alternative approaches to harnessing the therapeutic potential of the incretin system have been pursued—GLP-1 receptor agonists and DPP-4 inhibitors.

Two Alternative Approaches

The GLP-1 receptor agonists are designed to fulfill the role of native GLP-1 while exhibiting resistance to degradation by DPP-4, and are present for therapeutic use at supraphysiologic levels (equivalent to 6–10-fold normal GLP-1 levels). These drugs include exenatide (available since 2005), exenatide long-acting release (LAR), which is undergoing regulatory review by the U.S. Food and Drug Administration (FDA); and liraglutide, which is available in the United States, Europe, and Japan. Other drugs (AVE-0010 bid/ZP10, albiglutide, and taspoglutide/R1583) have recently entered phase III trials; their data will not be reviewed.

The DPP-4 inhibitors act to impair the activity of the DPP-4 enzyme, thereby increasing the half-life of endogenous GLP-1. Compared with the GLP-1 receptor agonists, DPP-4 inhibitors produce modestly elevated levels of GLP-1 and exert their effects principally through interaction with receptors on afferent nerves rather than through receptors on target organs.[40] The first of these drugs to enter the market was sitagliptin, which was approved in the United States in 2006. A second DPP-4 inhibitor, vildagliptin, has been approved for use in Europe; however, since its manufacturer is not pursuing approval in the United States, vildagliptin will not be discussed in detail. Saxagliptin has received recent European Medicines Agency and FDA approval, but U.S. approval of alogliptin has been delayed because of the requirement for an additional cardiovascular study. In December 2008, the FDA issued the recommendation that all therapies for the treatment of type 2 diabetes should provide evidence that they do not increase the risk of cardiovascular events. Hence, alogliptin will not be reviewed.

To identify relevant literature on the incretin-based therapies, a MEDLINE search (January 1985–November 2009) was performed by using the following key words: type 2 diabetes, incretin, GLP-1, DPP-4, liraglutide, exenatide, sitagliptin, and saxagliptin. Relevant references from the publications identified during this search were also reviewed. All studies that were published in the English language and that evaluated the safety and efficacy of incretin-based therapies were analyzed. Priority was given to randomized clinical trials and retrospective studies in clinical settings.

Pharmacology

Glucagon-Like Peptide-1 Receptor Agonists

Exenatide. This drug is a recombinant peptide based on exendin-4, which is found in the saliva of *Heloderma suspectum* (i.e., Gila monster lizard). Exenatide shares 53% of its amino acid sequence identity with human GLP-1 and functions as a full agonist of the GLP-1 receptor.[41] It is, however, more resistant to degradation by DPP-4 enzyme, due to the presence of a glycine residue on the penultimate NH_2 group.[42]

Studies investigating the pharmacokinetic profile of exenatide show that it reaches peak plasma levels at about 2 hours after subcutaneous injection, has a plasma half-life of 3–4 hours, and provides glucose reduction over 5–7 hours.[43, 44] This means that exenatide requires twice-daily dosing (0–60 min before breakfast and dinner) and exerts its predominant effect on PPG levels.[44] A new drug application for a long-acting (slow-absorption) formulation requiring once-weekly dosing (exenatide LAR) was submitted in May 2009. In March 2010, a response letter was issued by the FDA requesting the finalization of the product labeling, risk evaluation and mitigation strategy, and clarification of existing manufacturing processes. Preliminary data indicate that exenatide LAR may have better efficacy than twice-daily exenatide.[45] Exenatide is renally excreted,[46] and although no dosage adjustment is needed in cases of mild or moderate renal impairment, exenatide is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease ([ESRD] i.e., chronic, irreversible renal failure). This advice follows the finding that single doses of exenatide 5 µg caused gastrointestinal adverse effects in patients with ESRD who were receiving dialysis.[47] Gastrointestinal adverse events in these patients may worsen renal function. In November 2009, the FDA issued guidance advocating caution when starting or uptitrating exenatide in patients with moderate renal impairment (creatinine clearance 30–50 ml/min).[48]

Elimination of exenatide is not dependent on hepatic function, however, and it is therefore not expected to interact with hepatically metabolized drugs as a result of competition for liver

enzymes. One way in which exenatide and other GLP-1 receptor agonists might interact with other drugs is through their effects on gastric motility and, hence, absorption kinetics. Studies examining the possibility of such an effect on digoxin, warfarin, and a statin do not suggest that their kinetics will be altered to a clinically meaningful extent by concomitant exenatide.[49–51]

Liraglutide. This GLP-1 receptor agonist is rather different from exenatide in its structure (Figure 2). It is an analog of human GLP-1 with 97% primary amino acid sequence identity, but with a fatty acid side chain attached through a glutamic acid linker.[52] This fatty acid structure enables reversible plasma albumin binding, which may contribute to the drug's partial resistance to DPP-4 degradation and its subsequent prolonged action.[53] The primary mechanism for prolonging the action of liraglutide, however, is thought to be through slowed absorption due to the self-association (as heptameric aggregates) of liraglutide molecules within the injection depot.[53] These heptamers are thought to be too large to pass through capillary membranes readily, so absorption is delayed pending the dissociation of liraglutide through dilution at the absorption site. Although liraglutide is partially resistant to DPP-4 degradation, elimination studies show that it is nevertheless degraded almost completely into small molecules by this enzyme and by endopeptidases, as with endogenous GLP-1.[54, 55] This means that its elimination is not dependent on hepatic or renal function, which may prove to be clinically advantageous.

Studies that investigated the pharmacokinetic profile of liraglutide have shown that it reaches peak plasma levels 9–12 hours after dosing by subcutaneous injection, with a subsequent mean elimination half-life of 11–15 hours.[56] Steady state is reached after 3 days, and therapeutic plasma liraglutide concentrations are observed for up to 24 hours after a single injection. These characteristics make liraglutide compatible with once-daily administration, and it may be possible to choose the dosing time without regard to meals.[56, 57] As with exenatide, drug-drug interaction studies have been performed to investigate liraglutide's potential to affect the kinetics of drugs that are sensitive to gastric transit time due to their absorption properties. Again, it was concluded that the effect of liraglutide on atorvastatin, lisinopril, digoxin, and griseofulvin was unlikely to be clinically relevant.[58]

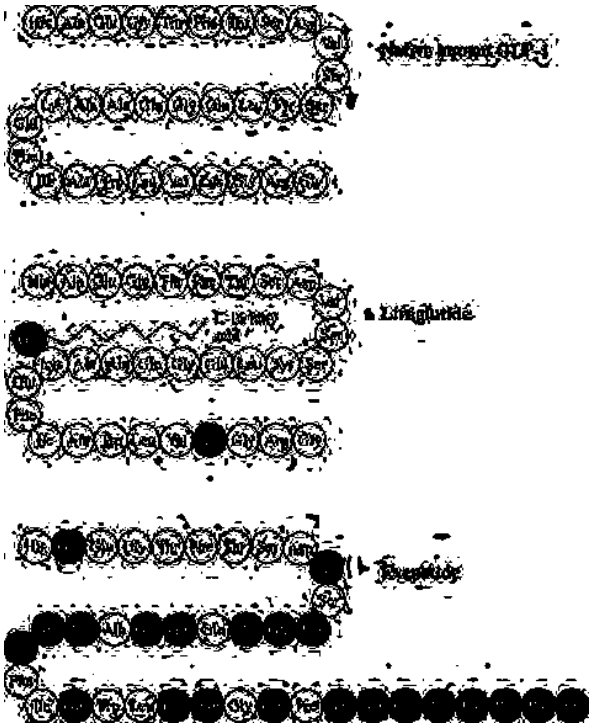

Figure 2. The structures of native glucagon-like peptide-1 (GLP-1), liraglutide, and exenatide. (From reference 52 with permission.)

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin. This drug is an orally absorbed small molecule that produces at least 80% inhibition of DPP-4 activity for 12 hours at doses of 50 mg or more, and for 24 hours at doses of 100 mg or more.[59] Therefore, the recommended dosage is 100 mg once/day. Compared with placebo, sitagliptin results in at least a 2-fold increase in postprandial GLP-1 levels, both after single doses and at steady state, reducing postprandial glycemia and not causing hypoglycemia.[59, 60] Steady state is reached after about 2 days. Inhibition of glucagon secretion is also seen with DPP-4 inhibition, but this class of drugs does not seem to affect gastric motility to the extent of the GLP-1 receptor agonists, possibly because of the relatively modest increase in GLP-1 signal that DPP-4 inhibition alone induces.[61] This might also account for the observation that weight tends to remain unchanged rather than reduced in response to DPP-4 inhibition. It is also worth noting that the DPP-4 enzyme degrades other peptides besides the incretins, including cytokines and chemokines,[61] and inhibition of

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