CLINICAL Viewpoint

Expanding Treatment Options for Diabetes: GLP-1 Receptor Agonists

Advancements in Diabetes Management: A Canadian Diabetes Steering Committee Report

Report 2 Objectives

After reading this report, physicians will be able to:

1. Understand the incretin system and its role in regulating glucose homeostasis;
2. Critically assess the similarities and differences between GLP-1 receptor agonists and DPP-4 inhibitors; and
3. Describe the potential advantages and disadvantages of GLP-1 receptor agonists in relation to existing antihyperglycemic agents.

In this Report

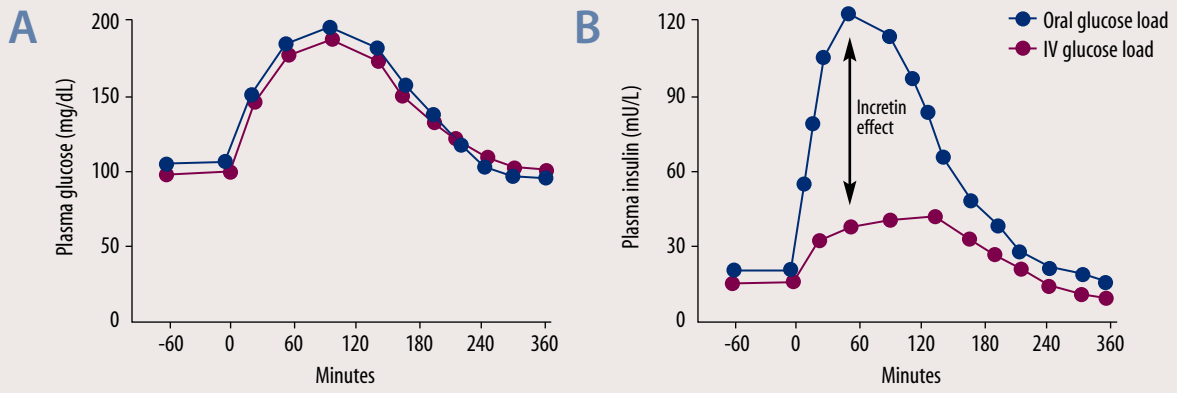
Diabetes management is continually evolving. Our current toolbox of oral antihyperglycemic agents includes many different drugs that work in different ways. A new class of therapies (termed "incretin agents") has shown promise in the management of diabetes through novel mechanisms of action. This report will provide an introduction to agents in this new class and contrast them with currently available therapies.

Presenting the Incretin System

At any given level of plasma glucose, pancreatic beta cells secrete more insulin if glucose is given orally rather than intravenously (Figure 1).[1] This difference is termed the "incretin effect." This amplification of insulin secretion when glucose is ingested orally is mediated by peptide hormones (incretins) secreted from the intestinal tract. The physiologically important incretins are glucose-dependent insulinotropic polypeptide or GIP (secreted by jejunal K cells) and glucagon-like peptide-1 or GLP-1 (secreted by ileal L cells and colon).[2-5] Both GIP and GLP-1 have short half lives—they are rapidly metabolized by the enzyme dipeptidyl peptidase-4 (DPP-4) leading to their inactivation.[6] In individuals with diabetes, the biological effects of GIP are completely lost and GLP-1 levels are significantly lower than in non-diabetics; however the functional effects of GLP-1 are retained.[2,7] For this reason, GLP-1 has been more extensively studied in the context of drug development. Therapeutic incretin agents include modified and unmodified biological compounds which imitate the structure and function of the naturally occurring gastrointestinal hormones, or substances that inhibit the inactivation of these hormones.

FIGURE 1

The Incretin Effect: Intravenous and Oral Glucose Loads Result in Identical Glucose Responses (A), But Varied Insulin Responses (B)[1]



Oral glucose administered at time = 0 minutes.

The Multiple Glucoregulatory Benefits of GLP-1 (Figure 2)

Glucose-dependent insulin secretion. As stated above, GLP-1 augments the insulin response to ingested glucose (Figure 3B). However, this enhancement of insulin secretion only occurs in the presence of elevated blood glucose. Thus, agents that mimic the effect of GLP-1 are unlikely to cause significant hypoglycemia.

Glucagon secretion. In addition to glucose-dependent insulin secretion, a very important physiological effect of GLP-1 is the inhibition of glucagon secretion (Figure 3C).[11] Glucagon has an important role in stimulating glucose production and release from the liver (especially in the fasting state). In non-diabetic individuals, glucagon is suppressed with food ingestion. In individuals with diabetes, glucagon secretion is not suppressed postprandially. The continued effect of glucagon on liver glucose production contributes significantly to hyperglycemia.[2]

Gastric emptying and satiety. GLP-1 can also modulate factors associated with nutrient ingestion and absorption. It has been shown to promote the feeling of satiety and to decrease food intake in humans.[12] GLP-1 also delays gastric emptying, which has the effect of slowing down glucose absorption into the blood stream.[13] In fact, GLP-1-based therapies are weight-neutral or associated with weight loss. Other antihyperglycemic therapies—such as insulin sensitizers and secretagogues—may actually result in weight gain.[14]

Beta cell function. *In vitro*, GLP-1 has been shown to promote differentiation of cells into beta cells and to reduce beta cell death.[15,16] Both observations are intriguing as they raise the possibility that GLP-1 could prevent beta cell death and actually produce new beta cells in humans. These findings are in contrast with *in vitro* data which seem to indicate that overstimulation of the beta cells by insulin secretagogues might actually lead to beta cell death in the long term.[16]

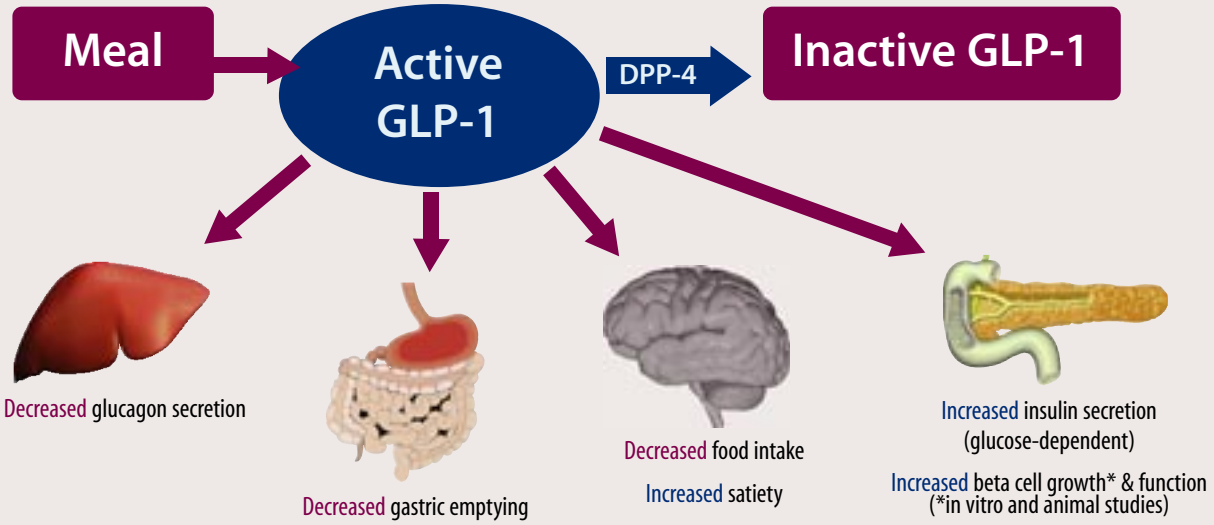
Diabetes management is continually evolving. Our current toolbox of oral antihyperglycemic agents includes many different drugs that work in different ways. A new class of therapies (termed "incretin agents") has shown promise in the management of diabetes through novel mechanisms of action.

Harnessing the Therapeutic Potential of GLP-1

GLP-1 has a half-life of approximately 1-2 minutes. It is rapidly cleaved by the enzyme DPP-4 and eliminated by renal excretion.[17] Many of the effects of GLP-1 observed in clinical research (Table 1) were

FIGURE 2

Diagrammatic Overview of GLP-1 Physiological Actions[8-10]



obtained under conditions of continuous GLP-1 infusion. Given the short half-life of GLP-1 and the impracticality of continuous infusion in clinical practice, other means to achieve the effects of GLP-1 have been investigated. This research has led to the development of DPP-4 inhibitors and GLP-1 receptor agonists, both of which work to restore GLP-1 action in type 2 diabetics.

DPP-4 inhibitors prevent the inactivation of GLP-1 by DPP-4 enzymes, thereby prolonging GLP-1 availability in the body. There are two DPP-4 inhibitors currently available in Canada: sitagliptin and saxagliptin. Both agents have demonstrated significant A1C reductions compared to placebo and a weight neutral effect.[18-21] Sitagliptin and saxagliptin are dosed once daily due to their long half-lives. The most commonly reported adverse event associated with DPP-4 inhibitors is nasopharyngitis.[18,20] There have been rare reports of pancreatitis in patients receiving DPP-4 inhibitors.[22]

GLP-1 receptor agonists. Another way to prolong the effects of GLP-1 is the development of GLP-1 receptor agonists that are resistant to enzymatic inactivation by DPP-4. Although GLP-1 receptor agonists are not yet available in Canada, two such agents have been extensively studied: exenatide and liraglutide. Exenatide is a protein derived from the saliva of a lizard known as the Gila monster and possesses approximately 53% homology to human GLP-1. Development of anti-exenatide antibodies has been noted in some patients using this agent.[23] Liraglutide is a natural human GLP-1 receptor agonist which has been modified slightly to protect it from inactivation by DPP-4.[23] Liraglutide has 97% homology to endogenous GLP-1 and, as a result, greatly reduced antibody development has been observed with liraglutide administration compared to exenatide.[24-26]

Overall, both liraglutide and exenatide have demonstrated significant A1C reductions of up to 1.5% and 1.11%, respectively.[25,27] Further, the GLP-1 receptor agonists have also demonstrated weight reduction, while DPP-4 inhibitors are reportedly weight neutral.[28,29] Liraglutide and exenatide have

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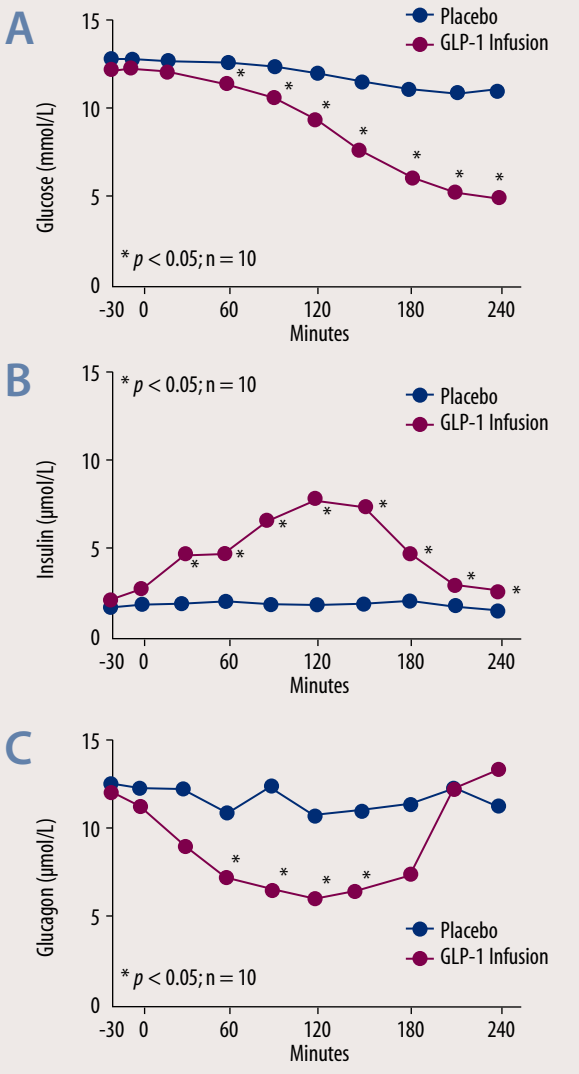
FIGURE 3

Glucoregulatory Effects of GLP-1 IV Infusion on Plasma Glucose Levels (A), Plasma Insulin Levels (B), and Plasma Glucagon Levels (C)[11]



also shown beneficial effects on blood pressure (BP); this parameter is not indicated as an endpoint in the published phase III trials of DPP-4 inhibitors among people living with diabetes.[25,30-32]

Preliminary data have demonstrated that GLP-1 receptor agonists have a beneficial effect on beta cell function.[33,34] However, further studies are required to evaluate whether this will impact diabetes disease progression.

GLP-1 receptor agonists are generally well-tolerated; transient gastrointestinal symptoms are the most commonly reported adverse events.[24-29,34,35] Similar to DPP-4 inhibitors, there have also been rare reports of pancreatitis in patients receiving GLP-1 receptor agonists.[24,28,34-36] However, there are too few reports to establish whether or not there is a cause-and-effect relationship between the development of pancreatitis and treatment with DPP-4 inhibitors or GLP-1 receptor agonists. Additionally, patients with type 2 diabetes have a 2.8-fold greater risk of developing acute pancreatitis compared to the general population.[37]

Many of the effects of GLP-1 observed in clinical research (Table 1) were obtained under conditions of continuous GLP-1 infusion. Given the short half-life of GLP-1 and the impracticality of continuous infusion in clinical practice, other means to achieve the effects of GLP-1 have been investigated.

Strengths and Weaknesses of Currently Available Antihyperglycemic Agents

Each class of antihyperglycemic agents possesses its own mode of action. No class of agents is able to address all of the abnormalities associated with diabetes. Accordingly, most individuals living with diabetes are prescribed a combined regimen of antihyperglycemic agents. Unfortunately, these regimens eventually fail as they are unable to address the progression and evolution of the disease. Moreover, they may expose patients to a host of adverse events including weight gain and hypoglycemia.[14,38]

Blood glucose reduction. In the absence of contraindications, metformin is recommended as the first-line therapy for diabetes. The recommendation for metformin's use first line is based upon its efficacy in lowering A1C and its relatively good adverse effect profile. If target A1C is not met with metformin alone another agent from a different class—such as a sulfonylurea (SU) or a thiazolidinedione (TZD)—should be added. Both SUs and TZDs have shown similar efficacy to metformin in terms of A1C lowering.[14] SUs offer a less durable reduction in A1C

TABLE 1

Overview of GLP-1 Actions

1. Glucose-dependent insulin secretion
2. Inhibits glucagon secretion
3. Delays gastric emptying
   - improved control of postprandial glucose homeostasis
4. Promotes feeling of satiety and reduced food intake
   - results in weight loss
5. Possible action: promotes beta cell growth and function
   - increases insulin synthesis
   - increases insulin sensitivity
   - promotes beta cell differentiation
   - promotes beta cell survival

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when compared to metformin and TZDs. The reduced durability is attributed to a decrease in beta cell function and mass related to disease progression.[39] Meglitinides are insulin secretagogues similar to SUs. The meglitinides provide lower A1C reductions but are associated with better postprandial glucose (PPG) reductions. Alpha-glucosidase inhibitors and DPP-4 inhibitors both lower glucose via gastrointestinal-related mechanisms but do so to a lesser extent than the other antihyperglycemic agents. Like the meglitinides, alpha-glucosidase inhibitors and DPP-4 inhibitors also show improved efficacy in reducing PPG levels.[14]

Impact on body weight. SUs and TZDs are frequently associated with weight gain. Metformin, alpha-glucosidase inhibitors and DPP-4 inhibitors are generally weight neutral.[14]

Risk of developing hypoglycemia. Hypoglycemia remains a major problem for patients trying to achieve glycemic targets. Insulin secretagogues—particularly SUs—are most frequently associated with an increased risk of hypoglycemia.[14] Patients prescribed SUs should be counseled about the recognition and prevention of hypoglycemia.

Incidence of adverse effects. As with other medications, oral antihyperglycemic agents are associated with adverse effects. Alpha-glucosidase inhibitors and metformin are the antihyperglycemic agents most frequently associated with gastrointestinal adverse effects which are usually mild to moderate in intensity.[14] In addition to gastrointestinal adverse effects, metformin is rarely associated with lactic acidosis. TZDs have been associated with fluid retention, edema, congestive heart failure and osteoporosis.[14] In selecting an appropriate treatment regimen for people with diabetes, the adverse effect profile must be weighed against the potential benefits.

Effect on beta cell function. TZDs and incretin-based therapies have shown potential for improvements in beta cell function.[40] However, long-term data are still required to assess the impact on disease progression and the clinical management of diabetes.

Summary: Bridging the Gap in Diabetes Care

Current oral antihyperglycemic agents are useful in the management of type 2 diabetes. Unfortunately, no single agent is able to address all the pathophysiological abnormalities of diabetes. Therefore new, effective agents with novel mechanisms of action are a welcomed addition to our treatment options. Incretin-based therapies stimulate insulin secretion only when glucose is elevated; thus, significantly decreasing the risk of hypoglycemia. Agents in this class are either weight neutral (DPP-4 inhibitors) or are associated with significant weight loss (GLP-1 receptor agonists). In view of the progressive beta cell dysfunction in type 2 diabetes, interventions that might improve or preserve beta cell function are particularly intrigu-

ing. Incretin-based therapies show promise in this area; however, long term data are still required to assess the clinical relevance of *in vitro* observations.

In the Next Report:

The next report will address GLP-1 receptor agonists in more detail.

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