

HOW DO INCRETIN-BASED THERAPIES FIT INTO THE TREATMENT ALGORITHM?

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed “incretins,” are gut-derived peptide hormones released from intestinal K and L cells into the bloodstream in response to ingested nutrients. They greatly augment the insulin response of the pancreas to an oral glucose load. In patients with T2DM, particularly those with more long standing disease and poorer glycemic control (HbA_{1c} ~8–9%), the GLP-1 response to glucose and mixed meal challenges is decreased, but GIP secretion is unchanged when compared to healthy subjects. Also, acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in these patients. The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form). For this reason, GLP-1 analogues, also known as “incretin mimetics” (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. All incretin mimetics are peptides and need to be administered by subcutaneous injection. Exenatide has a half-life of ~3 h and has been approved for administration (twice-daily injections) to type 2 diabetic patients inadequately controlled with oral antidiabetic agents, and lowers HbA_{1c} by about 0.7–1%. Liraglutide has a half-life of 12–14 h (suitable for once-daily administration) and can lower HbA_{1c} between 1–1.5%. GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, TZDs, and insulin. DPP4 inhibitors, which are oral agents that inhibit the breakdown of endogenous GLP-1, also lower HbA_{1c} levels. They are well tolerated, weight neutral, and have a very low risk of hypoglycemia. Based on these advantages, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of type 2 diabetes.

Keywords: Incretin-based therapy; diabetes mellitus

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WHAT ARE “INCRETINS” AND WHAT IS THEIR RELEVANCE TO DIABETES?

Glucagon-like peptide-1 (GLP-1) and glucose-dependent

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insulinotropic polypeptide (GIP), termed “incretins,” are gut-derived peptide hormones released from intestinal K and L cells into the bloodstream in response to ingested nutrients. They greatly augment the insulin response of the pancreas to an oral glucose load, an effect not seen with an intravenous glucose infusion. These incretins increase insulin secretion in a glucose-dependent manner through activation of their specific receptors on β -cells.

In patients with T2DM, particularly those with more long standing disease and poorer glycemic control (HbA_{1c} ~8–9%), the GLP-1 response to glucose and mixed meal challenges is decreased, whereas GIP secretion is unchanged when compared to healthy subjects. However, acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in these patients (Chia et al 2008)¹. Additional beneficial effects of GLP-1 on endocrine pancreatic islets are that it 1) supports the synthesis of proinsulin to replenish insulin stores in β -cells; 2) reduces the rate of β -cell apoptosis when islets are incubated in a toxic environment (glucotoxicity, lipotoxicity, cytotoxic cytokines); and 3) promotes differentiation of precursor cells with the ability to develop into β -cells and proliferation of β -cell lines, and in whole animals (rodent studies), this leads to an increased β -cell mass within a few days or weeks. Furthermore, GLP-1 can lower glucagon concentrations, i.e., induce β -cells to respond again to the inhibitory action of hyperglycemia, while leaving the counterregulatory glucagon responses undisturbed, as in the case of hypoglycemia (Nauck et al 2009)². Additional activities of GLP-1 are the deceleration of gastric emptying, which slows the entry of nutrients into the circulation after meals, a reduction in appetite, and earlier induction of satiety, leading to weight reduction with chronic exposure. Renal effects (promotion of sodium and water excretion, as well as neuro- and cardioprotective properties of GLP-1, have also been described. In contrast, exogenous GIP, even at supraphysiological doses, has markedly reduced insulinotropic actions with little or no glucose-lowering effects in T2DM. Therefore, therapeutic strategies for T2DM within the incretin field focused on the use of GLP-1, and not GIP (Drucker et al 2006)³.

WHAT IS INCRETIN-BASED THERAPY?

The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form) caused by rapid proteolytic degradation and inactivation through the ubiquitous enzyme DPP-4 and renal elimination, making it difficult to use therapeutically. For this reason, **GLP-1 analogues, also known**

as “**incretin mimetics**” (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. A common feature of all incretin mimetics is that they are peptides and need to be administered by subcutaneous injection. They bind to and activate the GLP-1 receptor and display the full array of biological (antidiabetic) activity known for/characteristic of (CTT) Collaborators Study has affirmed this approach of dyslipidemia treatment. This large meta-analysis of more than 90,000 patients confirmed the central role of lowering LDL cholesterol 6. In this meta-analysis of 14 large-scale statin trials, a 1-mmol/L reduction in LDL-cholesterol reduced the incidence of major coronary event by 23% and the incidence of CHD death by 19% over 5 years. In the high-risk group with pre-existing CHD, a 1-mmol/L (or 38 mg/dL) reduction in LDL-activate the GLP-1 receptor and display the full array of biological (antidiabetic) activity known for/characteristic of GLP-1. Within the group of incretin mimetics, differences are seen with respect to amino acid homology in comparison to native human GLP-1, and in pharmacokinetic characteristics, such as elimination of half-lives, and so forth. Novel attempts have aimed at developing compounds, or preparations, with a longer duration of action, and less frequent administration (e.g. once-weekly). The two available forms of incretin mimetics currently available are exenatide and liraglutide. Exenatide is a synthetic form of a natural peptide found in the saliva of *Heloderma suspectum* (a big venomous lizard found in the USA and Mexico) with amino acid sequence homology with GLP-1. Exenatide has a half-life of ~3 h and has been approved for administration (twice-daily injections) to type 2 diabetic patients inadequately controlled by oral antidiabetic agent, and has been shown to lower Hb A1c by about 0.7-1% (Nielsen et al 2004)⁴. Recently developed liraglutide, synthesised by attaching a free fatty acid to a slightly modified GLP-1 molecule, is characterised by a half-life of 12–14 h (suitable for once-daily administration) and can lower HbA1c between 1-1.5%.

Another method of exploiting the antidiabetic potential of GLP-1 is by **inhibiting its proteolytic degradation and inactivation through the action of DPP-4**. Several agents have been identified that are able to inhibit DPP-4 activity (in serum) by >85% and preserve GLP-1 secreted from endogenous sources (mainly in response to meal ingestion) in its intact biologically active forms, thus leading to doubled or tripled incremental responses (Ahren et al 2004)⁵. Sitagliptin, vildagliptin, alogliptin and saxagliptin have been approved as DPP4-inhibitors. All these agents, in general, have a modest HbA1c-lowering effect between 0.5-1% (Renee et al 2007)⁶.

WHAT ARE THE POTENTIAL ADVANTAGES OF INCRETIN-BASED THERAPY?

One of the most significant advantages is the glucose-dependent nature of its insulinotropic effects, which means that

incretin-based therapies amplify physiologic insulin secretion and are associated with very low rates of hypoglycemia. In addition to this, incretin-based therapies do not cause weight gain. In fact, GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, thiazolidenideones (TZDs), and insulin. DPP-4 inhibitors are weight neutral (Renee et al 2007)⁶. Post prandial glucose excursions are also significantly reduced with incretin-based therapy, probably in part due to their effect at modulating glucagon secretion.

Additional novel features include possible positive effects of some incretin-based therapies on the β -cell. This has been shown in several animal models and in-vitro studies on islet cells, but clinical data is scarce. GLP-1 analogues improve some parameters of β -cell function during treatment; however, this effect has not been shown to be sustained one year after treatment with exenatide (Bunck et al 2009)⁷. Even less data regarding beta cell preservation is available with DPP4-inhibitors.

Some mechanistic studies have even suggested the cardio-protective activity of GLP-1. Similar effects may be present with GLP-1 analogues. Clinical trials have shown effects of exenatide and liraglutide on surrogate cardiovascular parameters such as systolic blood pressure, triglycerides, and brain natriuretic peptide (Ban et al 2008)⁸. Long-term studies proving cardiovascular benefit are necessary for both incretin mimetics and DPP-4 inhibitors.

WHAT ARE THE POTENTIAL DISADVANTAGES OF INCRETIN-BASED THERAPY?

Dose-dependent nausea and vomiting are the most frequently reported adverse events with incretin-mimetics, particularly with exenatide. Up to 57% may have nausea and 17% vomiting, which generally peaks during the initial 8 weeks of treatment and declines thereafter. Liraglutide seems to have lower rates of gastrointestinal complaints. Some cases of pancreatitis have been reported with incretin-mimetic therapy, but it is not clear whether they have occurred at a higher rate than expected for an obese type 2 diabetic population. A somewhat higher rate of nasopharyngitis may be seen in patients on DPP4 inhibitors, and occasional elevations in liver enzymes have been reported with vildagliptin. Overall however, DPP4 inhibitors are very well tolerated, with low absolute rates of adverse events (Renee et al 2007)⁶.

HOW DOES INCRETIN-BASED THERAPY FIT INTO THE CURRENT TREATMENT ALGORITHMS?

This new class of medication is a welcome addition to our existing pharmacological therapies against Type 2 diabetes and its associated severe morbidity and mortality. Meta-analyses have shown that incretin-based therapy in adults with Type 2 diabetes is moderately effective in improving glycemia, with greater reductions in postprandial glucose. This preferential improvement of postprandial glycemia addresses an important limitation of currently available pharmacologic therapies and provides an alternative to our limited options for targeting post-prandial glycemia. In contrast to nearly all available hypoglycemic agents which cause weight gain, GLP-1 analogues have a favorable effect, and DPP4 inhibitors a neutral effect on weight.

As such, the main advantages which incretin-based therapies offer over traditional oral agents and insulin, is in terms of both convenience and reduced side effects, especially with regard to the expected frequency of hypoglycemia and weight gain. Based on these, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of type 2 diabetes.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a joint treatment recommendation with an algorithm for the stepwise escalation of therapeutic steps in the course of type 2 diabetes. Based on evidence from clinical studies and on available cost-effectiveness data, they divided therapy into Tiers 1 (“well-validated therapy”) and 2 (“less-well validated therapy”). Tier 1 therapy included lifestyle modification with initial metformin monotherapy, followed by the addition of basal insulin or sulphonylurea if glycemic goals were not met. Incretin-mimetics and DPP-4 inhibitors were not included in the first tier of this algorithm because of their generally still limited clinical data and/or relative expense. Instead, they were included in Tier 2 of “less well-validated therapy” to be considered in selected clinical settings, including obese patients or those with a low tolerance for hypoglycemia (Nathan et al 2009)⁹.

The American Association of Clinical Endocrinologists (AACE) also published a treatment algorithm for patients with Type 2 diabetes. Their approach was slightly different from that adopted by the ADA/EASD algorithm. The AACE panel gave issues like patient compliance and adverse events such as hypoglycemia and weight gain higher priority over expense or long term clinical data. As such, incretin based therapy was

elevated to first line therapy alongside more established players like metformin, sulphonylureas, thiazolidinediones and alpha glucosidase inhibitors (Rodbard et al 2009)¹⁰.

CONCLUSIONS

While new medications are often prized and quickly embraced, recent experiences with other drugs like rosiglitazone may have taught us a lesson of caution with newer agents which still have limited clinical data on long term effectiveness and safety. On the other hand, incretin-based therapy has shown to date that it certainly has several distinct physiologic and therapeutic advantages over currently available therapy. As such, it is rapidly becoming a very valuable addition to our armamentarium in our fight against the multifactorial and complex disease that is diabetes. At the end of the day, all the guidelines, despite their differences, reinforce the need of an individualised treatment approach for patients with Type 2 diabetes. As clinicians, it remains our call as to whether incretin-based therapy will be beneficial to each of our individual patients.

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LEARNING POINTS

- **Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), termed “incretins,” are gut-derived peptide hormones.**
 - **Acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in patients with Type 2 Diabetes**
 - **The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form) and for this reason, GLP-1 analogues, also known as “incretin mimetics” (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. All incretin mimetics are peptides and need to be administered by subcutaneous injection.**
 - **DPP4 inhibitors, which prevent the breakdown of endogenous GLP-1, can also enhance GLP-1 levels and help lower plasma glucose.**
 - **GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, TZDs, and insulin, while DPP4 inhibitors are weight neutral.**
 - **The glucose-lowering effect of incretin based therapy is glucose dependent; in other words, the risk of hypoglycemia is very low.**
 - **Based on these advantages, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of Type 2 Diabetes.**
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