Comparing Current Therapies, Incretins and Incretin Mimetics in Type 2 diabetes Management

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ABSTRACT

The benefits of tight glycaemic control in landmark clinical trials in conjunction with aggressive blood pressure and lipid control in preventing / postponing diabetic complications have now been well established. In view of the complex and progressive nature of the disease, only 15-25% of type 2 diabetic subjects are able to maintain a target haemoglobin A1c of less than 7% that too at the cost of hypoglycaemia and weight gain. Further, type 2 diabetic patients have often lost 50% of β-cell function at the time of diagnosis of the disease and glycaemic deterioration occurs over ensuing years regardless of therapy.

Glucose-dependent insulinotropic polypeptide stimulated by oral nutrient ingestion represents potent insulin secretagogues responsible for the augmentation of insulin release. The observation that the patients with type 2 diabetes exhibit a significant reduction in the magnitude of meal-stimulated insulin release underlies the interest in determining whether defective incretin release or resistance to incretin action contributed to the β-cell dysfunction in diabetic subjects. Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, apart from the potent glucose lowering properties also have remarkable effects on β-cell proliferation and cytoprotection and may be helpful in preventing progression to β-cell failure in diabetic subjects. GLP-1R agonists and DPP-IV inhibitors in ongoing clinical trials suggest that one or both classes of agents may ultimately be approved for the treatment of type 2 diabetes. Furthermore, there remains intense interest in developing GLP-1 secretagogues or GLP-1 receptor activators. Strategies focused on enhancing incretin action are likely to receive increasing attention if the first generation of GLP-1R agonists and DPP-IV inhibitors are approved for the treatment of type 2 diabetes.

INTRODUCTION

Recognition of the benefits of strict glycaemic control in type 1 diabetes and the landmark United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto Study have clearly shown that glycaemic control matters not only in type 1, but also in type 2 diabetes. Diabetic complications can be prevented by improved glycaemic control and in conjunction with adequate control of blood pressure and lipids. Since type 2 diabetes has a long asymptomatic phase, it is not uncommon to observe minimal or overt complications at the time of diagnosis. The “ticking clock” hypothesis of Haffner et al that macrovascular coronary artery disease precedes the onset of type 2 diabetes while microvascular complications accompany the diagnosis of type 2 diabetes has put the onus of early recognition of abnormal glucose tolerance on individuals at risk to develop diabetes. Our ability, however, to reach the rather low long-term glycaemic targets is, at best, limited in view of the complex and progressive nature of the disease and with hitherto available therapeutic strategies, only 15-25% are able to achieve a good glycaemic control.

Type 2 diabetes is characterized by insulin resistance and impaired β-cell secretory function. Loss of acute insulin response to a carbohydrate load occurs when fasting plasma glucose levels reach 115 mg/dl and by the time it reaches to 140 mg/dl, 75% of β-cell function is lost. The deposition of amyloid has been associated with progressive loss of β-cell function and mass. Insulin resistance in the hepatocyte and peripheral tissues leads to unrestrained hepatic glucose production (HGP) and diminished glucose uptake and utilization. It could be due to defects in insulin receptor binding, decreased numbers of receptors or post-receptor attenuation of insulin action. In addition, the high circulating free fatty acid levels further aggravate insulin resistance and adversely affect β-cell secretion, a phenomenon known as lipotoxicity.

Type 2 diabetes may be present 9 to 12 yrs before diagnosis and a study in Pima Indians indicates that defects in both insulin secretion and action occurs early in the course of the disease and also predicts the transition from normal to IGT and from IGT to diabetes. Because of its progressive nature, in UKPDS study, it was clearly shown that the percentage of patients who achieved a HbA1c level lower than 7% with diet alone or monotherapy with insulin, a sulfonylurea or metformin decreased from 50% at 3 yrs to less than 25% at 9 yrs of follow-up. Further, patients...
with Type 2 diabetes have often lost 50% of β-cell function at diagnosis of diabetes and over ensuing years is associated with glycaemic deterioration regardless of therapy. The difficulty in maintaining HbA1c at target levels may be related to several behavioral factors (e.g. lack of adherence to diet, exercise, medication) but primarily reflects the underlying progressive decline in β-cell function.

The newer drugs already in use, or in the process of being developed for management of type 2 diabetes are classified into (1) insulin secretagogues (2) insulin sensitizers (3) drugs delaying gastrointestinal glucose absorption (4) drug acting on intermediary metabolism to reduce hepatic glucose output and (5) insulin mimetic drugs (Table 1).

A comparative evaluation of various oral drugs used in treatment of type 2 diabetes mellitus is shown in Table 2.

**WHAT IS THE OPTIMAL TREATMENT REGIMEN?**

Initial therapy is shifting from secretagogues and α-glucosidase inhibitors, which effectively lower only plasma glucose concentrations, to insulin sensitizers-drugs that lower plasma glucose levels while also reducing cardiac risk factors - that it is hoped will lead to a decrease in the incidence of cardiac events. Metformin acts as insulin sensitizer by inducing weight loss through decreasing appetite and, perhaps, by increasing the mobilization of glucose transporters in the muscle, however, the sensitizing effects of metformin are much weaker than those of TZDs.

**TREATMENT WITH INSULIN SENSITIZERS**

**TZDs**
TZDs shift adipocytes from the peritoneum to subcutaneous space and increase FFA storage in the subcutaneous adipocytes and produce an improvement in the profile of cardiac risk factors associated with insulin resistance. Besides TZDs therapy have been shown to be associated with decrease in the thickness of tunica media and intima of carotid arteries and decrease in the incidence of restenosis of the coronary arteries following angioplasty.

**TZDs and β-Cell Function**
The most compelling reason to use TZDs in type 2 diabetic subjects is its ability to preserve or improve β-cell function. In the β-cell, increased triglyceride levels due to defective activity of leptin leads to an increase in intracellular FFAs which increase the activity of nitric oxide synthase and thus raise nitric oxide levels accelerating β-cell apoptosis. TZD therapy provide β-cell stabilization or even rejuvenation and decrease proinsulin-to-insulin ratio. It also increases endogenous insulin levels and in the Troglitazone In Prevention of Diabetes (TRIPOD) study, troglitazone treatment resulted in >50% decrease in the development of diabetes. The characteristics of TZD-induced fluid retention and its mechanism remain poorly defined but may be due to the potentiation of insulin effects on sodium and water retention. The fluid retention should not necessarily be equated with worsening HF, and these patients should not

<p>| <strong>Table 1 : Target drug therapy for type 2 DM</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Functional Class</strong></th>
<th><strong>Drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Insulin secretagogues</td>
<td>Sulfonylureas (Repaglinide, Nateglinide), Meglitinide derivatives (Repaglinide, Nateglinide), GLP-1, Amylin antagonists</td>
</tr>
<tr>
<td>2. Insulin sensitizers</td>
<td>Metformin, Thiazolidinediones (Troglitazone, Rosiglitazone, Pioglitazone), Anti-obesity drugs</td>
</tr>
<tr>
<td>3. Inhibitors of GI glucose absorption</td>
<td>α-glucosidase inhibitors (Acarbose, Miglitol), Amylin analogue (Pramlintide)</td>
</tr>
<tr>
<td>4. Inhibitors of intermediary metabolism</td>
<td>Antilipolytic and Antihyperlipidemic agents, Fatty acid oxidation inhibitors</td>
</tr>
<tr>
<td>5. Insulin-mimetic drugs</td>
<td>Insulin analogues, IGF-1, Vanadium salts</td>
</tr>
</tbody>
</table>

* Functional class 1,4 and 5 have hypoglycemic, while 2 and 3 have anti hyperglycemic mode of response.

<p>| <strong>Table 2 : Comparison of different oral drugs used in management of type 2 diabetes</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Decrease in FPG(mg/dl)</strong></th>
<th>Sulfonylureas</th>
<th>Metformin</th>
<th>Thiazolidinediones</th>
<th>Acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in HbA1c(%)</td>
<td>1.5-2.0</td>
<td>1.5-2.0</td>
<td>0.5-1.0</td>
<td>0.7-1.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>No effect or mild ↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>HDL-C</td>
<td>No effect</td>
<td>↑</td>
<td>↑</td>
<td>No effect</td>
</tr>
<tr>
<td>LDL-C</td>
<td>No effect</td>
<td>↓</td>
<td>↑</td>
<td>No effect</td>
</tr>
<tr>
<td>Body weight</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
<td>No effect</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>No effect</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Hypoglycemia, Wt. gain, GI intolerance, Lactic acidosis,</td>
<td>Wt. gain, Fluid retention, Hepatotoxicity</td>
<td>GI intolerance</td>
<td></td>
</tr>
</tbody>
</table>

A comparative evaluation of various oral drugs used in treatment of type 2 diabetes mellitus is shown in Table 2.
necessarily be deprived of its usefulness as long as they are being closely monitored for weight gain, fluid retention, and other signs and symptoms of decompensated HF.38

**Metformin and TZD Combination Therapy**

Even though the United Kingdom Prospective Diabetes Study (UKPDS) showed a decrease in the incidence of cardiac events with metformin use in overweight patients with type 2 diabetes, metformin is a weak insulin sensitizer when compared with a TZD.20 The combination therapy of metformin and TZD in small doses increases the efficacy, minimize side effects, improve compliance and save costs compared with a large dose of one drug.49 Increased efficacy results from the action of metformin on the liver complementing the actions of the TZD and stabilizing or rejuvenating pancreatic β-cell. Metformin is however, contraindicated in all patients with heart failure as its use is associated with an increased risk of potentially lethal lactic acidosis.41

However, the major advantage of using an insulin sensitizer alone or in combination with another sensitizer is the absence of severe or even moderate degree of hypoglycemia and better glycemic control. A lower level of HbA1c has been shown to be associated with reduced cardiac mortality and total mortality.42-45 If once-daily combination of metformin and TZD does not achieve the target level of HbA1c, the insulin sensitizers should be administered twice daily. If building up to a maximum twice-daily regimen does not achieve the desired glycemic goals, then a secretagogue (i.e., a sulfonylurea, repaglinide, or nateglinide) should be added.

**Triple Oral Therapy**

First described in 1998, triple oral therapy consisting of metformin, a TZD, and a sulfonylurea has achieved target HbA1c levels provided that a third agent was not added when the difference between the current and target HbA1c values was >1.5%.46 During the 6 months after troglitazone was replaced with rosiglitazone in a group of patients receiving triple therapy, 24% had their secretagogue dose reduced or stopped, 7% discontinued suggesting a continued improvement in β-cell function,47 and at 3-year 70% maintained HbA1c of 6.9% with significant increase in endogenous insulin production.48 At 5-year 62% of these patients continued to have an average HbA1c of 7.1%.49 A double-blind study of therapy failure with metformin and sulfonylurea showed that patients randomized to the addition of rosiglitazone had a return of first-phase insulin response, an effect that did not occur in patients randomized to the addition of insulin.49

**α-glucosidase inhibitors**

Because α-glucosidase inhibitors lower only postprandial50 and not fasting plasma glucose levels, the efficacy of these agents is limited to a 0.5% to 1.0% decrease in HbA1c value.51,52 The acarbose has been associated with a significant reduction in the risk of cardiovascular disease and hypertension50 (STOP-NIDDM Trial). Side effects such as excess flatulence due to undigested carbohydrate fermented by bacteria in the large bowel are troublesome to most patients. However, patients who are renally compromised can attain a 5-times higher peak plasma drug concentration, possibly leading to hepatotoxicity.52,53 Therefore, in patients whose serum creatinine concentration is >2.0 mg/dL, α-glucosidase inhibitors should not be used.

**SECRETAGOGUES**

All secretagogues cause the release of more insulin at any given plasma glucose level by closing the energy-sensitive potassium channel in the cell membrane of the β-cells. This leads to β-cell depolarization and an influx of calcium, resulting in increased exocytosis and release of insulin.55,56 The first-and second-generation sulfonylureas have a more prolonged attachment to the sulfonylurea receptor, causing a more prolonged release of insulin, and are more likely to be associated with hypoglycemia.57 In addition, glyburide has been shown to decrease the counter-regulatory release of both glucagon from the pancreas and growth hormone from the pituitary gland, which further increases the risk of hypoglycemia.58

Another problem with first- and second-generation sulfonylureas is the closing of energy-sensitive potassium channels not only in the all-membrane of pancreatic β-cell but also in cardiomyocytes. The process of ischaemic preconditioning during myocardial ischaemia does not occur when potassium-adenosine triphosphate (k.ATP) are blocked with the result the ischaemia is sustained and risk of myocardial damage increases, when it may have been averted.59 At the Mayo Clinic, coronary angioplasty after acute MI was found to be associated with increased 48-hour mortality in patients with diabetes who were treated with sulfonylurea.59 Another study showed a decrease in the ejection fraction of ischaemic myocardium with glyburide but not with insulin.60 The results of these studies confirm that ischaemic preconditioning is blocked in both non-diabetic and diabetic myocardium by glyburide but not the third-generation glimepiride.61,62

A recent retrospective study53 suggested that attenuation of electrocardiographic ST-segment elevation during moderate-sized acute MI occurs in diabetic patients treated with sulfonylurea drugs. During acute MI with creatinine phosphokinase (CPK) levels between 500 and 1,000 mg/dL, those patients treated with sulfonylurea drugs were found to have a reduced magnitude of ST elevation as compared with subjects with diabetes who were not treated with sulfonylurea drugs. These patients were less likely to meet the standard ECG criteria for thrombolytic therapy. Large-scale evaluations are necessary to further clarify the impact of sulfonylurea treatment and evaluation of acute MI in this population.55

**MAINTAINING GLYCEMIC CONTROL WITH EXOGENOUS INSULIN**

When triple therapy fails, the addition of a subcutaneous insulin injection is needed to regain glycemic control. A premixed insulin, preferably of rapid-acting insulin with a compatible intermediate-acting insulin (e.g., insulin analogue lispro 75/25 or aspart 70/30 mix), may be administered with the evening meal, or the long-acting insulin glargine may be injected at bedtime. To maximize the potential of these insulins, start with a small dose (0.2 per kg or 10 IU) and titrate by 20% increments at intervals of 2 to 3 days until either the fasting plasma glucose value is ≤ 110 mg/dL or nocturnal or early morning hypoglycemia occurs.

If daytime glycemic control cannot be maintained by means of oral agents and a single injection of insulin, options include...
expanding the regimen to two injections of a premixed insulin or administering a preprandial dose of short-acting insulin 1 to 3 times daily in addition to glargine at bedtime. At the same time, discontinuation of the secretagogue is suggested and maintenance of a single or dual insulin-sensitizer regimen is recommended; insulin therapy for type 2 diabetes, especially in obese patients, offers better glycemic control when combined with an insulin sensitizer than when administered as monotherapy.

EXPLORING NEW THERAPIES IN DIABETES - INCRETIN MIMETICS

The observation that food ingestion or enteral glucose administration provoked a greater stimulation of insulin release compared with similar amounts of energy (glucose) infused intravenously led to the development of the incretin concept. Hence, it was postulated that gut-derived signals stimulated by oral nutrient ingestion represent potent insulin secretagogues responsible for the augmentation of insulin release when energy is administered via the gut versus the parenteral route. Although several neurotransmitters and gut hormones possess incretin-like activity, the considerable evidence from immunoneutralization, antagonist and knockout studies suggest that glucagon-like peptide (GLP-1) represent the dominant peptides responsible for the majority of nutrient-stimulated insulin secretion.

Incretin : Synthesis, Secretion and degradation

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are members of the glucagons peptide superfamily. Ingestion of a mixed meal or a meal enriched with specific fats and complex carbohydrates is particularly effective in stimulating GIP and GLP-1 release in human subjects. Circulating levels of GIP (1-42) are normal or slightly increased in type 2 diabetic subjects in the basal or postprandial state. In contrast, subjects with diabetes or impaired glucose tolerance exhibit modest but significant reductions in levels of meal stimulated circulating GLP-1. Furthermore, meal-induced increase in GIP and GLP-1 secretions are inversely correlated with the extent of insulin resistance detected in human subjects.

Biological actions of GLP-1

- Stimulate insulin secretion and suppresses glucagons secretion
- Slows gastric emptying and reduces food intake

Table 3 : Exploring New therapies in Diabetes-Incretin mimetics.

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th>GLP-1 Analogues</th>
<th>Extendin Analogues</th>
<th>DPP-IV Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- NN 2211</td>
<td>- AC 2993</td>
<td>LAF 237</td>
</tr>
<tr>
<td></td>
<td>- CJC-1131</td>
<td>- AC 2993</td>
<td>MK 0431</td>
</tr>
<tr>
<td></td>
<td>- DAC-GLP-1</td>
<td>- ZP-10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Exendin-4 (Exenatide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Exendin-4 Long acting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 : Properties and biological actions of GIP and GLP-1

<table>
<thead>
<tr>
<th>GIP</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>42-amino acid peptide</td>
<td>30/31-amino acid peptide</td>
</tr>
<tr>
<td>Released from duodenum</td>
<td>Released from distal small bowel and colon</td>
</tr>
<tr>
<td>NH₂-terminal inactivation by DPP-IV</td>
<td>NH₂-terminal inactivation by DPP-IV</td>
</tr>
<tr>
<td>Stimulates insulin secretion</td>
<td>Stimulates insulin secretion</td>
</tr>
<tr>
<td>Minimal effect on gastric emptying</td>
<td>Inhibits gastric emptying</td>
</tr>
<tr>
<td>No effect on glucagon secretion</td>
<td>Inhibits glucagon secretion</td>
</tr>
<tr>
<td>No regulation of satiety and weight gain</td>
<td>Promotes expansion of β-cell mass</td>
</tr>
<tr>
<td>Promotes expansion of β-cell mass</td>
<td>Normal GIP secretion in diabetic subjects</td>
</tr>
<tr>
<td>Normal GIP secretion in diabetic subjects</td>
<td>Defective GIP response in type 2 diabetes</td>
</tr>
<tr>
<td>Defective GIP response in type 2 diabetes</td>
<td>Preserved GLP-1 response in type 2 diabetes</td>
</tr>
</tbody>
</table>

- Increases β-cell mass and maintains β-cell function
- Improves insulin sensitivity and enhances glucose disposal

Single or repeated subcutaneous injection of native GLP-1 decrease blood glucose in human subjects and the glucose lowering effect is no longer evident 1-2 h after peptide injection. Continuous IV or subcutaneous infusion of GLP-1 has been shown to be highly effective in lowering blood glucose in diabetic subjects when compared with peptide infusion for 16 hrs however, rapid degradation and clearance of native and exogenously administered GLP-1 have spurred the clinical development of degradation resistant GLP-1 analogues with longer duration of action in vivo.

Exendin-4, a naturally occurring 39-aminoacid GLP-1 agonist isolated from the salivary gland venom of the lizard Heloderma suspectum, exhibits 53% aminoacid identity to mammalian GLP-1. Intravenous infusion of exendin-4 lowered fasting and postprandial blood glucose in normal healthy volunteers and was associated with a 19% reduction in caloric consumption. Exendin-4 treatment (0.08-10 µg/kg subcutaneous injection at 11:00 p.m., in association with...
Table 5: Characteristics of DPP-IV inhibitors and GLP-1R agonists

<table>
<thead>
<tr>
<th>DPP-IV inhibitors</th>
<th>GLP-1R agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally available</td>
<td>Injectable</td>
</tr>
<tr>
<td>Multiple targets</td>
<td>Single known GPCR target</td>
</tr>
<tr>
<td>GLP-1 PK favorable</td>
<td>Higher levels of GLP-1 achievable, but narrow PK profile</td>
</tr>
<tr>
<td>Short-versus long-acting</td>
<td>Longer acting – days to weeks</td>
</tr>
<tr>
<td>Less potent agents</td>
<td>More potent glucose lowering</td>
</tr>
<tr>
<td>Drug overdose nontoxic</td>
<td>Drug overdose problematic</td>
</tr>
<tr>
<td>No central nervous system side effects</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Less defined side effect profile</td>
<td>Well-described and tolerable side effect profile</td>
</tr>
</tbody>
</table>

GLP-1 Receptors

Islet β-cell

GLP-1

GLP-1R agonists
Albumin-conjugated GLP-1
Long-acting GLP-1 analogues
Gene therapy

DPP-IV

Secretagogues
Nutraceuticals

Gut endocrine cell secreting GLP-1

Secretagogues
Nutraceuticals

Fig. 2: Potentiation of incretin action for the treatment of Type 2 diabetes

Inhibition of DPP-IV for the treatment of type 2 diabetes

DPP-IV, the principal enzyme responsible for incretin inactivation, in a single-dose escalation study of P32/98 in healthy male volunteers improved oral glucose tolerance with increase levels of GLP-1. A 4-week trial of NUP DPP 728 in type 2 diabetic subjects (mean entry HbA1c of ~ 7.6%) produced significant glucose lowering in mean HbA1c to 6.9%. DPP-IV inhibition of gastric emptying and reduced levels of circulating glucagons. NN2211 has been tested in phase 2 clinical trials.

GLP-1R agonists and DPP-IV inhibitors: Unanswered questions

GLP-1 exhibits several distinct advantages desirable in a therapeutic agent for treating type 2 diabetes (Table 4). GLP-1R agonists produce remarkable effects on β-cell proliferation and cytoprotection and therefore its potential to prevent progression to β-cell failure in diabetic subjects is intriguing, but largely undocumented.

DPP-IV inhibitors will be able to achieve the same pharmacological elevation in levels of circulating GLP-1 (Figure 2) compared with injectable GLP-1 based drugs, and are likely to be less potent compared with injectable GLP-1 R agonists (Table 5).

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