

## Review Article

# Incretin-Based Antidiabetic Agents: A New Option for Type-2 Diabetes Mellitus.

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### Abstract

Type 2 Diabetes Mellitus (T2DM) is a complex disease with the co-existence of several pathophysiological abnormalities. Both microvascular and macrovascular complications are the main causes of morbidity and mortality, which develops due to endothelial dysfunction. Upregulation of reactive oxygen species, chronic inflammatory and hypercoagulable states are the pathologic basis of vascular dysfunctions in T2DM. To overcome all these abnormalities, different classes of antihyperglycaemic agents have developed. Unfortunately none is able to show satisfactory glycaemic control and to modulate vascular dysfunction. Incretin hormones are secreted from intestine during meal, which enhance insulin secretion and inhibit glucagon secretion from the pancreas. The incretin effect is severely reduced or absent in T2DM. Incretin-based new antidiabetics, both Dipeptidyl Peptidase-4 (DPP-4) inhibitors (Saxagliptin, Sitagliptin, Vildagliptin) and Glucagon Like Peptide-1 (GLP-1) analogs (Exenatide) are now being used globally. They are almost equally effective as conventional antidiabetics like Sulphonylureas (SU), Metformin (MET), Thiazolidinediones (TZD) and insulin when given as monotherapy or combined with SU, MET or TZD as second line agent. Incretin-based agents do not cause hypoglycaemia, produce weight loss in spite of weight gain and do not retain salt or water and almost no gastrointestinal (GIT) symptoms. The agents correct vascular dysfunctions and dyslipidaemia and can be given in elderly and renal impaired patients.

### Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycaemia caused by absolute or relative deficiency of insulin. T2DM comprises 95% of total diabetes which is caused by a combination of insulin resistance and impaired pancreatic Beta-cell function leading to relative insulin deficiency. The prevalence of diabetes in UK is around 4%, but is higher in the

Middle and Far East (e.g. 12% in urban areas of the Indian sub-continent)<sup>1</sup>. Possibly by the year 2025, India shall have approximately 57.2 million diabetes, the maximum number of diabetics in any one country<sup>2</sup>. About 15-20% of T2DM patients present with macro/micro vascular complications at the time of diagnosis<sup>3</sup>. From clinical perspective, T2DM is a cardiovascular disease, supported by a range of epidemiologic, postmortem, and cardiovascular imaging studies. Vascular wall dysfunction particularly endothelial dysfunctions, has been posited as a "common soil" linking dysglycemic and cardiovascular diseases. Vascular wall dysfunction promoted by environmental and metabolic triggers has been associated with up regulation of reactive oxygen species, chronic inflammatory and hypercoagulable states, which ultimately leads to atherosclerosis and cardiovascular disease<sup>4</sup>. Non pharmacological approach (e.g. with Diet and Discipline) to control DM are ill sustained, with <10% patients achieve acceptable long term glycaemic control. Among oral antidiabetics, SU and MET are popular and widely used. Currently available SU have gradually increasing secondary failure rates reaching 50% at the end of 5 years; though the initial response is good in 70-75% of patients. Moreover these drugs cause hypoglycaemia and weight gain. MET although used alone or in combination with SU, GIT intolerance limits their use in many patients<sup>5</sup>. So it is not easy to achieve the goal of persistent and

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tight metabolic control, partly due to limitations of currently available modalities of treatment and partly due to patient's noncompliance with non pharmacological and pharmacological prescriptions<sup>6</sup>. In this situation TZD and later on Incretin-based antidiabetic agents came to play roles in the management of DM. TZD have significant side-effects, Troglitazone had to be withdrawn because of hepatotoxicity and newer TZDs are avoided in patients with liver dysfunction and in cardiac failure. Although Pioglitazone reduces Myocardial Infarction and Stroke, Rosiglitazone slightly increases the chance of acute ischemic events<sup>1</sup>. GLP-1, an incretin hormone, and synthetic GLP-1 receptor agonists represent promising new areas of research and therapeutics in the struggle not only against T2DM but also against the cardiovascular morbidity and mortality associated with it. In a number of small trials in humans, as well as in preclinical and in vitro studies, both native GLP-1 and GLP-1 receptor agonists have demonstrated positive effects on a range of cardiovascular disease. Reductions in triglycerides and free fatty acids have also been observed<sup>4</sup>. So incretin-based antidiabetics are now becoming popular globally due to its different behavior in carbohydrate metabolism. Here we will try to explore these drugs as new options for diabetic patients.

#### ***Incretins and their roles in carbohydrate metabolism:***

The incretin hormones include GLP-1 and gastric inhibitory peptide (GIP). GLP-1 is secreted by ileal L-cells and is dependent on the presence of nutrients in the lumen of the small intestine. Once in the circulation, GLP-1 has a half life of less than 2 minutes, due to rapid degradation by the enzyme DPP-4. Known physiological functions of GLP-1 includes<sup>7</sup>:

- \* Increases insulin secretion from the pancreas in a glucose-dependent manner.
- \* Decreases glucagon secretion from the pancreas by engagement of specific G protein-coupled receptor.
- \* Increases insulin-sensitivity in both alpha cells and beta cells
- \* Increases beta cells mass by promoting proliferation/neogenesis and prevent their decay
- \* Inhibits acid secretion and gastric emptying in the stomach.
- \* Decreases food intake by increasing satiety.
- \* Promotes insulin sensitivity.

Both GLP-1 and GIP hormones contribute to insulin secretion from the beginning of a meal and their effects are progressively amplified as plasma glucose concentrations rises. They potentiate glucose-induced insulin secretion and may be responsible for up to 70% of postprandial insulin secretion<sup>8</sup>. These actions are mediated through GLP-1 receptors (GLP-1Rs), although GLP-1R independent pathways have also been reported. Other than pancreatic islets, GLP-1Rs are also present in central and peripheral nervous system, gastrointestinal tract, heart and vasculature. Indeed, accumulating data from both animal and human studies suggest a beneficial

effect of GLP-1 and its metabolites on myocardium, endothelium and vasculature, as well as potential anti-inflammatory and anti-atherogenic actions. This suggests a potential cardio protective effect beyond glucose control and weight loss<sup>8</sup>. The current interest in the incretin hormones is due to the fact that the incretin effect is severely reduced or absent in patients with T2DM<sup>9</sup>. In such patients, the secretion of GIP is near normal, but its effect on insulin secretion is severely impaired. GLP-1 secretion, on the other hand is impaired but its insulinotropic and glucagon-suppressive actions are preserved. The impaired action of GLP-1 and GIP in T2DM may be partly restored by improved glycaemic control<sup>10</sup>. The reduced incretin effect is believed to contribute the impaired regulation of insulin and glucagon secretion in T2DM, and thus exogenous GLP-1 administration may restore blood glucose regulation to near normal levels. Clinical strategies therefore include the development of metabolically stable activators of the GLP-1 receptor (GLP-1 analog) and inhibitors of DPP-4, the enzyme that destroys native GLP-1 almost immediately. Orally active DPP-4 inhibitors and the metabolically stable activators, Exenatide, are now on the market, and numerous clinical studies have shown that both principles are associated with durable antidiabetic activity<sup>10,11,12</sup>.

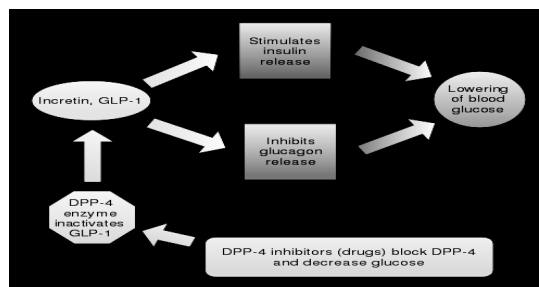


Figure 1: Relation of DPP-4, GLP-1 and glucose homeostasis.

Following incretin-based antidiabetic agents are found now a day:

1. DPP-4 inhibitors- Saxagliptin, Sitagliptin, Vildagliptin, Alogliptin, Linagliptin.
2. GLP-1 analogs- Exenatide, Liraglutide, Taspoglutide, Lixisenatide.

***Vildagliptin:*** Vildagliptin, a selective DPP-4 inhibitor, has been shown to produce significant reductions in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels when used as monotherapy (0.6-1%) or in combination with other glucose-lowering agents (0.7%). So it appears to be a promising agent for the management of type 2 diabetes<sup>13</sup>. As initial combination therapy, Vildagliptin have gained a great deal of attention in the context of beneficial effects on Beta-cell function with lowered risk of weight gain and hypoglycemia<sup>14</sup>. Vildagliptin as an add-on to Metformin have shown significant improvements in glycaemic control. The combination being well tolerated and associated with low risks of hypoglycaemia and adverse

effects on weight or lipid levels. Good tolerability and glycaemic control have also been observed as an add-on treatment to SU, TZD, or insulin treatment. Improved Beta-cell function and glycaemic control have been shown with Vildagliptin in subjects with impaired glucose tolerance and in T2DM patients with mild hyperglycemia, with some evidence in the latter suggesting the potential for modifying disease course<sup>15</sup>. Monotherapy trials with Vildagliptin also have shown that significant HbA<sub>1c</sub> lowering is accompanied by body weight and lipid lowering effects, low risk of edema, and low risk of hypoglycemia. For older patients and patients with chronic renal insufficiency, Vildagliptin have an advantage because they are unlikely to cause hypoglycemia<sup>16</sup>. It is also beneficial in the month of Ramadan in respect of less chance of hypoglycaemia. While the drug is still not approved for use in the US, it was approved in Feb 2008 by European Medicines Agency for use within the European Union and is listed on the Australian PBS with certain restrictions.

**Sitagliptin:** This DPP-4 enzyme-inhibiting drug is used either alone or in combination with other oral antihyperglycaemic agents for treatment of T2DM. Its bioavailability is 87%, half life is 8 to 14 hours and excreted through kidney<sup>17</sup>. The co-administration of Sitagliptin and biguanide compound reduce hepatic glucose production and slightly improves insulin sensitivity thus improves glucose control without inducing hypoglycaemia or weight gain<sup>18</sup>. The Sitagliptin/Metformin 50mg/500mg and 50mg/1000mg fixed dose combination tablets are bioequivalent to co-administration of corresponding doses of Sitagliptin and Metformin as individual tablets and support bioequivalence to the Sitagliptin/Metformin 50mg/850mg tablet strength<sup>19</sup>. Sitagliptin reduced HbA<sub>1c</sub> by 0.5% to 0.8%, compared with placebo, whether used as monotherapy or in combination with another agent. As initial combination therapy with Metformin, Sitagliptin have demonstrated reductions in HbA<sub>1c</sub> of 1.9%<sup>20</sup>. Sitagliptin was approved by the U.S. Food and Drug Administration (FDA) on October 17, 2006 and On April 2, 2007, the FDA approved an oral combination of Sitagliptin and Metformin marketed in the USA<sup>21</sup>.

**Saxagliptin:** Study show that Saxagliptin combination therapy improves HbA<sub>1c</sub> levels compared with placebo, particularly in patients with high HbA<sub>1c</sub> at baseline, long duration of disease, low baseline creatinine clearance. The study results also show that the Saxagliptin plus Metformin combination is a good candidate for initial therapy in drug-naive patients treated for as long as 72 weeks. It has a low risk of hypoglycemia as well. Saxagliptin monotherapy is a promising option for patients with renal impairment. It is well-tolerated with a safety profile similar to that of placebo<sup>22</sup>. Dhillon et al found oral Saxagliptin significantly improve mean HbA<sub>1c</sub> levels, relative to placebo, in treatment-naive patients with T2DM and combination therapy with Saxagliptin 5 mg once daily and Metformin was more effective than Saxagliptin or Metformin monotherapy<sup>23</sup>. Regarding

tolerability both monotherapy and combination therapy with other agents was generally well tolerated in clinical trials. Saxagliptin reduces HbA<sub>1c</sub> by 0.5% to 0.8%, compared with placebo, whether used as monotherapy or in combination with another agent. As initial combination therapy with Metformin and Saxagliptin have demonstrated reduction in HbA<sub>1c</sub> of 2.5%<sup>20</sup>. The FDA approved Saxagliptin on July 31, 2006.

**Cancer risk of DPP-4 inhibitors:** The DPP-4 enzyme is known to be involved in the suppression of certain malignancies, particularly in limiting the tissue invasion of these tumours. Inhibiting the DPP-4 enzymes may allow some cancers to progress<sup>24</sup>. A study of DPP-4 inhibition in human non-small cell lung cancer (NSCLC) concluded that DPP-4 functions as a tumor suppressor, and its down regulation may contribute to the loss of growth control in NSCLC cells<sup>25</sup>. The risk of cancer suppression with DPP-4 down-regulation applies to all the DPP-4 inhibitors on the market.

**Exenatide:** It is an incretin mimetic approved in April 2005 in USA for the treatment of T2DM. Exenatide is administered as a subcutaneous injection in the abdomen, thigh, or arm, 30 to 60 minutes before the first and last meal of the day. Currently developed a long-acting-release (LAR) formula of the drug, which can be injected once per week are now being trialed and showing equal efficacy with twice daily regimen. Madsbad S. et al found once weekly GLP-1 receptor analogues are promising option for the treatment of type 2 diabetes although their efficacy may not be superior to once daily analogue liraglutide<sup>26</sup>. It can be use as an adjunctive therapy to MET, SU, TZD to achieve adequate control of blood glucose. Use with insulin, Meglitinides and alpha-glucosidase inhibitors has not been studied. Some physicians are using Exenatide as primary monotherapy; an indication approved by the FDA October 30, 2009 as announced by Eli Lilly and Co. Diamant et al compared Exenatide's efficacy profile with that of insulin glargine, as an adjunctive antidiabetic agent for patients with T2DM with suboptimal glycaemic control despite maximum doses of oral blood-glucose-lowering drugs. Exenatide not only improved glycaemic control, it also induced weight loss and improvement of metabolic variables without increasing the frequency of hypoglycaemic events<sup>27,28</sup>. Insulin replacement frequently causes weight gain and can not maintain postprandial peak. Exenatide twice daily may be effective in these cases specially in obese group<sup>29</sup>. Regarding tolerability and pharmacokinetic/ pharmacodynamic relationships, 5 and 10 µg Exenatide may be considered for T2DM<sup>30</sup>. The main side effects of Exenatide use are belching, diarrhea, heartburn, indigestion, nausea, vomiting, dizziness, headache, and feeling of jittery. Drug interactions include delayed or reduced concentrations of Lovastatin, Paracetamol and Digoxin, although this has not been proven to alter the effectiveness of these medications. So Exenatide offers a novel treatment option for patients with T2DM who are

refractory to MET or SU therapy or both, specially those who are obese.

### Conclusion:

Incretin- based antidiabetics, both GLP-1 analog and DPP-4 inhibitors may be used as monotherapy or in combination with first line oral antidiabetics. Use with insulin is not yet established although trial is going on. Exenatide is an injectable preparation but is not substitute to insulin. To reduce weight in obese or overweight diabetics, these agents are more effective than first line oral antidiabetics. They don't produce hypoglycaemia, so useful for elderly diabetics and in the month of Ramadan. Drugs can also be used in renal impairment. Despite of above mentioned beneficial effect, cost effectiveness should also be considered before prescribing for an individual patient.

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