What the future holds for gliptins

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ABSTRACT
Gliptins have revolutionised the treatment of Type 2 Diabetes Mellitus, addressing the hyperglycemia through its effects on the alpha and beta cells of the pancreas. In this article, we review the extra-glycemic effects of gliptins on central nervous system, cardiovascular biology and the bone health and concerns regarding pancreatitis and pancreatic cancer.

Key words: Gliptins, cancer, bone health

INTRODUCTION
Despite an increasing number of therapeutic options, optimal management of hyperglycemia in patients with type 2 diabetes (T2D) remains an elusive goal for a majority of patients. Gliptins have revolutionized the treatment of T2D, addressing the hyperglycemia through its effects on the alpha and beta cells of the pancreas. In addition, gliptins have extra-glycemic effects on central nervous system, cardiovascular biology, and the bone health.

Role in pre-diabetes
The progressive natural history of diabetes is evidenced by, amongst other pathogeneses, a progressive decline of incretin effect. This opens up an exciting avenue of modifying the natural history of diabetes using the gliptins. To date, there are two studies investigating the effect of monotherapy with DPP-4 inhibitors in pre-diabetes: In a 12-week double-blind placebo-controlled trial in individuals with impaired glucose tolerance (IGT), vildagliptin induced a reduction of prandial glucose excursions and an increase of b-cell function accompanied by increase of both glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), and a decrease of glucagon secretion. In another study in individuals with impaired fasting glucose (IFG), vildagliptin improved both insulin sensitivity and b-cell function, leading to improved postprandial glycemia. These preliminary results are encouraging enough to provide the rational for testing in the future DPP-4 inhibitors as potential candidates for the prevention of T2D.

Gliptins in pediatric and adolescent diabetes
Patients with type 1 diabetes have significantly elevated postprandial glucagon secretion. Gliptins improve HbA1c by several mechanisms, including increasing GLP-1 and GIP concentrations, which decreases postprandial rises in glucagon in both type 1 and type 2 diabetes. There are reports in literature of use of gliptins, specifically sitagliptin, in adults with type 1 diabetes or in those with absolute insulin deficiency. Specifically, sitagliptin may have an independent role in the regulation of hepatic glucose output, glycogenesis, gluconeogenesis, glycolysis, or peripheral (skeletal muscle or adipose tissues) glucose uptake different from that of insulin or glucagon action. Alternatively, it may have a novel glycemic effect, such as inhibiting glucose absorption by the intestine. Sitagliptin also has been used in patients of type 1 diabetes following islet transplant procedure, in which the study subjects did gain some level of insulin independence. Although still not indicated for use in type 1 diabetes, the studies do

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provide an insight in the future possibility of utilizing the modification of incretin axis in the management of type 1 diabetes. Studies are underway to assess safety and efficacy of sitagliptin as an initial monotherapy for treatment of T2D in pediatric population.

**Gliptins and cardiovascular biology**

Short-term exposure to high glucose induces DPP-4 activity in microvascular endothelial cells. Although the precise biological role of DPP-4 in the cardiomyocyte, endothelial, or coronary smooth muscle cell requires further study, DPP-4 is also a circulating protein, and thus DPP-4 activity in the systemic and coronary circulation may influence intact levels of GLP-1 and other vasoactive DPP-4 substrates (like BNP, substance P, neuropeptide Y, peptide YY etc.) reaching the myocardium and vasculature. Although there is evidence of reduction in both systolic and diastolic blood pressure, availability of human data regarding the effects on atherosclerosis, heart failure, ischemic heart disease, and cardiomyopathy is insufficient. DPPIV is crucial for regulating the expression of factors related to steroid metabolism, such as Cyp51, Sc4mol, and Hsd17b2, and its deficiency or inhibition may cause dyslipidemia.[6]

There are various ongoing trials regarding the cardiovascular outcomes of use of gliptins [Table 1].

**Gliptins and bone health**

There is accumulating evidence that advanced glycation end products (AGEs) not only inhibit the proliferation and differentiation of osteoblasts but also induce activation of osteoblasts through the interaction with their receptor, RAGE (Receptor for AGE). Thus, AGE-RAGE axis may be involved in reduced bone density, contributing to an increased risk of bone fractures in T2D. Since DPP-4 inhibitors could play a protective role against vascular injury in T2D partly by attenuating the harmful effects of the AGE-RAGE axis,[7] the AGE-RAGE axis in the bone may also be a molecular target of DPP-4 inhibitors. Exogenous GLP-2 (also a DPP IV substrate) administration reduced serum and urine markers of bone resorption and increased hip BMD in a dose-dependent manner in post-menopausal women and improved spinal BMD in short-bowel patients with no colon.[8]

**Gliptins augment growth hormone secretion**

Growth hormone secretion is low in patients with obesity, insulin resistance, and hyperlipidemia. Growth hormone-releasing hormone (GHRH) has a half life of 5 minutes due to its rapid inactivation by DPPIV.[9] Gliptins may increase endogenous GH secretion by inhibiting degradation of GHRH by DPPIV. Clinical trial is underway to test the hypothesis that DPPIV inhibition simultaneously enhances GH secretion while improving blood glucoses and vascular function in patient populations with low GH and increased cardiovascular risk.

**Delaying diabetes in women with previous gestational diabetes**

Gestational diabetes mellitus (GDM) increases the risk of future diabetes. A randomized, double-blinded study

| Drug               | Study                                                                 | Dose                   | Primary outcome                                                                 | No. of patients |
|--------------------|-----------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------------|-----------------|
| Vildagliptin       | Effect of Vildagliptin on Left Ventricular Function in Patients with Type 2 Diabetes and Congestive Heart Failure | 50 mg twice daily      | LV function as determined via changes in ejection fraction                       | ~490            |
| Sitagliptin        | Sitagliptin Cardiovascular Outcome Study (0431--082 AM1) (TECOS)      | 50 or 100 mg/d oral tablet | Time to first confirmed cardiovascular event (nondiabetic MI, nonfatal stroke, or hospitalization for unstable angina) | ~14,000         |
| Alogliptin         | Cardiovascular Outcomes Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) | 6.25 or 12.5 or 25 mg/d oral tablet | Time from randomization to the first occurrence of a primary major adverse cardiac event (nondiabetic MI, nonfatal stroke, or cardiovascular death) | ~5,400          |
| Saxagliptin        | Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications (SAVAR-TIMI 53) | 2.5 or 5 mg/d oral tablet | Time to first confirmed cardiovascular event (nondiabetic MI, nonfatal ischemic stroke, or cardiovascular death) | ~16,500         |
| Linagliptin        | CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepride in Patients with Type 2 Diabetes | 5 mg/d oral tablet     | Time to the first occurrence of nondiabetic MI, nonfatal stroke, hospitalization for unstable angina, or cardiovascular death | ~6,000          |
Pancreatitis and pancreatic cancer: an area of concern with gliptin use

Available data from the US Food and Drug Administration’s (FDA) database of reported adverse events with use of sitagliptin (and exenatide), from 2004 to 2009, revealed increased odds ratio for reported pancreatitis 6-fold as compared with other therapies ($P < 2 \times 10^{-16}$). FDA has issued repeat safety alert in 2009 in view of 88 new cases of pancreatitis following sitagliptin use between 2006 and 2009.

Pancreatic cancer was also more commonly reported among patients who took sitagliptin (or exenatide) as compared with other therapies ($P < 0.008, P < 9 \times 10^6$). Moreover, because pancreatitis is a known risk factor for pancreatic cancer, long-term GLP-1 receptor activation might lead to increased risk for pancreatic cancer. Pancreatic carcinoma and chronic pancreatitis may become more apparent in the future when the patients would have had an exposure to gliptins for a long enough period. In addition, the available reports showing no relation of gliptins with pancreatic cancer were sponsored by pharmaceutical companies and arguably have a limited capacity to detect adverse outcomes.[90]

Glptins and cancer risk

DPPIV expression has been related with autoimmune arthritis, malignant cell prevention, and dissemination. It has been suggested that immunomodulatory effects of DPPIV inhibition might increase the risk of all cancers. Recent research in animal models links DPPIV inhibition to melanoma, prostate cancer, ovarian cancer, neuroblastoma, and lung cancer.[11]

However, suppressed DPPIV activity is a marker for early diagnosis of cancers; the reason of disassociation is not clear. Activation of RAGE is related to sideration of cancers. Since DPPIV inhibitors may be related to inhibition of RAGE activation, they may work as a cancer-protective agent in diabetes.

A study has been initiated by Japanese Investigators to evaluate the effects of DPPIV inhibitors (sitagliptin, alogliptin, and vildagliptin) on frequency of cancers and the underlying mechanism using AGE and RAGE before and 5 years after administration of DPP-IV inhibitors in patients with T2DM.

Conclusion

Although gliptins represent a new class of drugs in the available therapeutics for T2D, there are still grey areas, which need further investigation. Careful post-marketing surveillance for adverse effects and continued evaluation in longer-term studies is required to determine the role of this new drug class.

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