Evolution of Gliptins Over the Last 5 Years

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INTRODUCTION
Gliptins or dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of orally administered glucose lowering agents that have revolutionized the management of type 2 diabetes mellitus (T2DM).

Dipeptidylpeptidase-4 inhibitors represent a paradigm shift in the management of T2DM. In many ways, they have changed the way that diabetes and its management has so far been perceived by clinicians.

The crux of our understanding lies in the fact that Gliptins seek to favorably modulate a physiological mechanism, which is already in place in the human body; these agents augment the effect of the incretin hormones: peptides that are normally released from endocrine cells in the small intestinal mucosa in response to food to enhance meal-induced insulin secretion, and also to modulate glucagon lowering in fed state.

HISTORICAL PERSPECTIVE: INCRETIN DISCOVERY, TRIAL AND ERROR AND “REDISCOVERY”

The Early Years
The scientists who discovered secretin had already thought of the existence of a chemical excitant for the internal secretion of the pancreas. Data published between 1906 and 1935 tested the effect of injected or ingested duodenal extracts on blood glucose levels of animals and humans with equivocal results.

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Some Early Work in the Study of Incretins
William M Bayliss, Ernest H Starling, in 1902, published a paper entitled “The mechanism of pancreatic secretion”. This was a landmark in Gastrointestinal endocrinology. The authors proved that acid extracts of gut mucosa contained a hitherto undescribed factor, which stimulated via the blood stream the exocrine secretion of the pancreas and named this factor “secretin”.

In 1932, La Barre introduced for the first time the name incrétine (incretin) for a substance extracted from the gut, he was also the first to realize that his extract could be possibly used for the treatment of diabetes.

In 1964, the radioimmunoassay (RIA) technique showed that significantly more insulin was released after oral ingestion of glucose than after intravenous (IV) injection, in 1964 by Elrick et al. and McIntyre et al. Perley and Kipnis estimated that about half the insulin secreted after an oral glucose load was released by gut factors. Unger coined a term for this system “the enteroinsular axis”. In 1970, glucose-dependent insulinotropic polypeptide (GIP), and finally in 1985, glucagon-like peptide-1 (GLP-1) and its truncated form GLP-1(7-36) were recognized and named as true incretins.

Journey from the Laboratory Bench to the Front Row of Therapeutics
In humans, the two main physiologically important incretin hormones are: (1) GLP-1 and (2) GIP. They not only stimulate insulin secretion, but augment insulin stores by upregulating insulin gene expression, and also all the steps in the biosynthesis of insulin.

Another attractive facet of incretins is revealed by animal and in vitro studies, which seem to indicate that both these peptides have β-cell trophic effects, while GLP-1 also suppresses glucagon secretion and inhibits gastric emptying, appetite and therefore, caloric intake.

These peptides have, however, limited clinical usefulness themselves because they are rapidly degraded by the enzyme DPP-4, which severely limits their duration of action. The development of DPP-4-resistant GLP-1 analogues (incretin mimetics) and DPP-4 inhibitors (incretin enhancers) were logically proposed as an alternative means of exploiting the full therapeutic potential of this “incretin-axis”.

The inhibitors of the DPP-4 enzyme, which rapidly degrades the two major gastrointestinal hormones into inactive products, the “gliptins” increase the levels of the incretin hormones GLP-1 and GIP. The pharmacology of these drugs is based on very sound principles and this is why the gliptins are considered such attractive molecules for clinical use.

Evolution of the Gliptins
The first drug off the blocks was sitagliptin, the first DPP-4 inhibitor which was approved in 2006 and is now available for use globally including India. Vildagliptin followed soon, it is now available in the European Union (EU) and other countries since 2007, although approval by the United States Food and Drug Administration (USFDA) is still pending. The other marketed gliptins are saxagliptin (in 2009), alogliptin (in 2010, presently only in Japan) and linagliptin, which recently received approval in the US, Europe and Japan. Several other DPP-4 inhibitors like dutogliptin, gemigliptin, etc. are in various stages of development.

Compared to other oral hypoglycemic agents, gliptins produce similar reductions in blood glucose glycated hemoglobin (HbA1c) levels, but they offer several attractive clinical advantages.

A negligible risk of hypoglycemia, especially much lower than that observed with sulfonylureas, weight neutrality, contrasting favorably with the weight gain generally observed with sulfonylureas and thiazolidinediones (TZDs) are the key points, which make the gliptins
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stand out. Therefore, it is no surprise that this pharmacological class is expected to play an increasing role in the management of T2DM.8

The gliptins as a class also exhibit considerable heterogeneity amongst themselves in terms of substrate selectivity and pharmacokinetics of the different members of this family. Dipeptidyl peptidase-4 is a member of a complex gene family (DASH gene) many members of which also cleave structurally related peptides.

The DPP-4-related enzymes include: seprase, fibroblast activation protein (FAP), DPP-6, DPP-8 and DPP-9, attractin, quiescent cell proline dipeptidase, thymus-specific serine protease and DPP-4.

Since there is a structural similarity between the DASH family members, so enzymes like DPP-8 and DPP-9 (vildagliptin and saxagliptin), FAP (linagliptin) often get inhibited with the gliptins. Sitagliptin is the most selective DPP-4 inhibitor available at present. The clinical significance of inhibition of the DPP-4-related enzymes in vivo by these molecules is a matter, which is quite cloudy at present and further studies will need to be done to throw light on the matter. Linagliptin is the most potent DPP-4 inhibitor available. The pharmacokinetics of the different gliptins are shown in the Table 1.3–12

**Evolving Recent Data on the Clinical Efficacy of Gliptins**

Any new molecule(s), which enters the market is greeted with universal skepticism; however many doctors are slowly accepting the gliptins as a safe and effective group of drugs. As time passes and more experience is gleaned by the use of these drugs, the avenues of use, contraindications, beneficial as well as adverse effects will become better defined.

A study reveals DPP-4 inhibitors significantly reduced HbA1c at 24 weeks by 0.6% (0.5–0.7%) when compared with placebo; they showed a similar efficacy in monotherapy and in combination.13 They appear to be more effective in older patients with mild/moderate fasting hyperglycemia.14 A 24-week noninferiority trial comparing the efficacy of sitagliptin and metformin as monotherapy in T2DM patients (whose mean baseline HbA1c was 7.2), the mean changes in HbA1c were –0.43 and –0.57%, respectively. The between group difference was 0.14% (95% CI, 0.06–0.21%), demonstrating noninferiority of sitagliptin versus metformin.15 However, a head-to-head trial with metformin, vildagliptin failed to show noninferiority compared to metformin. After 52 weeks of treatment with vildagliptin and metformin, the reduction of HbA1c was (–1.0 ± 0.1%, P < 0.001) and (–1.4 ± 0.1%, P < 0.001), respectively from HbA1c baseline of 8.7.16

In another 18-week noninferiority trial comparing the efficacy of saxagliptin and sitagliptin in T2DM patients whose glycemia was inadequately controlled with metformin, the adjusted mean changes in HbA1c were –0.52% and –0.62%, respectively. The between group difference was 0.09% [95% confidence interval (Cl), –0.01% to 0.20%], demonstrating noninferiority of saxagliptin 5 mg versus sitagliptin 100 mg.17 In another randomized controlled trial (RCT) comparing linagliptin with sitagliptin, no significant difference was found between the two drugs. After 28 days of treatment with sitagliptin (100 mg OD) and linagliptin (5 mg OD) the weighted mean glucose change was found –26.1 mg/dL and –19.8 mg/dL, respectively.18 No major differences could be found between DPP-4 inhibitors regarding the reduction in HbA1c levels. For instance, in a meta-analysis of 12 trials with sitagliptin and 11 trials with vildagliptin, the weighted mean differences versus placebo were –0.79 (95% CI = –0.93 to –0.65) for sitagliptin and –0.67 (95% CI = –0.83 to –0.52) for vildagliptin.19

**Bodyweight**

A significant majority of patients with T2DM are overweight or obese in the western world. Many agents used to treat hyperglycemia (insulin, sulfonylureas, TZDs) are associated with weight gain, making management of overweight or obese patients challenging. As they are weight neutral, DPP-4 inhibitors represent a potentially important addition to the oral treatment options currently available. A recent meta-analysis of 12 RCT, it has been shown that as monotherapy, DPP-4 inhibitors were less effective in decreasing body weight than metformin (weighted mean difference 1.50, 0.94–2.18; I² = 69%) but not compared with GLP-1 agonists (1.56, 0.94–2.18; I² = 0%).20

**Cardiovascular Risk Factors**

Apart from their antihyperglycemic and weight neutral (or even mild weight-reducing) actions, which themselves confer cardiovascular (CV) benefits, DPP-4 inhibitors also reduce other CV risk factors: some recent trials have reported that they decreased systolic blood pressure (BP), improved postprandial lipid parameters, reduced high-sensitivity C-reactive protein (hsCRP) levels and improved endothelial dysfunction associated with their use.

Gliptins cause a modest reduction in BP independent of the blood glucose reduction. Recent evidences have suggested that the local actions of incretins may be mediated via their key role in

**Table 1 | Pharmacokinetics of gliptins**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Bioavailability</th>
<th>Half-life at clinically relevant doses</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>1–4 hours</td>
<td>87%</td>
<td>12.4 hours</td>
<td>38% protein bound</td>
<td>Not appreciably metabolized</td>
<td>Renal (80% unchanged)</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>1.5 hours</td>
<td>85%</td>
<td>2–3 hours</td>
<td>9.3% protein bound</td>
<td>69% metabolized mainly renal (inactive metabolite)</td>
<td>Renal (65% unchanged)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2 hour</td>
<td>&gt; 70%</td>
<td>2.2–3 hours (parent)</td>
<td>Low protein bound</td>
<td>Hepatic (active metabolite) CYP 3A4</td>
<td>Renal (12–29% as parent; 21–52% as metabolite)</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>1–3 hours</td>
<td>30%</td>
<td>113–130 hours</td>
<td>99% protein bound at 1 nm</td>
<td>Not appreciably metabolized</td>
<td>Feces (&gt; 70% unchanged)</td>
</tr>
</tbody>
</table>

Abbreviation: CYP 3A4, cytochrome P<sub>350</sub> 3A4

400
regulating natriuresis, thereby lowering BP, especially in individuals with salt-sensitive hypertension. A recent study provided the first evidence for a complex interactive hemodynamic effect of DPP-4 and angiotensin-converting enzyme (ACE) inhibition in humans. Indeed, sitagliptin lowered BP during placebo or submaximal ACE inhibition, whereas sitagliptin activated the sympathetic nervous system to diminish hypotension when ACE was maximally inhibited. Postprandial lipid levels are also influenced with DPP-4 inhibitors. Sitagliptin treatment for 6 weeks reduced postprandial plasma levels of triglyceride rich lipoproteins of both intestinal and hepatic origin. This effect is most likely mediated by increasing incretin hormone levels, reducing circulating plasma free fatty acid concentrations and improving insulin sensitivity and B-cell function. Four weeks vildagliptin treatment also has been shown to improve postprandial plasma triglyceride and apolipoprotein B–48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal. In an experimental study assessing changes in adipose tissue and skeletal muscle metabolism induced in T2DM patients, it has been shown that vildagliptin augmented postprandial lipid mobilization and oxidation, possibly by sympathetic activation rather than a direct effect on metabolic status. The mechanisms underlying the effects of DPP-4 inhibitors on postprandial lipid metabolism and their potential relationships with weight regulation remain to be explored. Reductions in hsCRP, soluble vascular cell adhesion molecule 1 and microalbuminuria have also been observed with the use of gliptins. In T2DM, microalbuminuria is not only considered as a marker of early nephropathy, but also as a marker of widespread endothelial dysfunction. Therefore, disappearance of microalbuminuria, when possible, may also reflect improvement of endothelial function with DPP-4 inhibitors reducing macrovascular disease as well.8

Results of a recent meta-analysis of 18 trials has shown that overall use of DPP-4 inhibitors was associated with a lower risk of adverse CV events [risk ratio (RR) = 0.48, 95% CI = 0.31–0.75, p = 0.001] and a lower risk of nonfatal myocardial infarction or acute coronary syndrome (RR = 0.40, 95% CI = 0.18–0.88, p = 0.02) compared to placebo or other oral hypoglycemic agents. Subgroup analysis by the studied DPP-4 inhibitors showed a significantly lower risk of adverse CV events with sitagliptin (RR = 0.37, 95% CI = 0.21–0.68, p = 0.001) but not with saxagliptin (RR = 0.64, 95% CI = 0.23–1.76, p = 0.39), alogliptin (RR = 1.73, 95% CI = 0.21–13.93, p = 0.61) or vildagliptin (RR = 0.50, 95% CI = 0.13–1.92, p = 0.31).

Risk of adverse CV events with DPP-4 inhibitor therapy was significantly lower compared to metformin (RR = 0.42, 95% CI = 0.20–0.87, p = 0.02) and other oral hypoglycemic agents including sulfonlurea, pioglitazone (except linagliptin) or insulin. Gliptins can be used as first or second add-on along with these drugs.

EVOLUTION OF THE IDEA OF GLIPTIN USE IN SPECIAL POPULATIONS

Renal Insufficiency

In such cases, the choice of antihyperglycemic agent is often limited with clinicians feeling comfortable with insulin usage, particularly regular variety in a judicious manner depending upon the degree of renal insufficiency (RI). With reduced glomerular filtration rate (GFR), toxicity of the oral drugs increases as the drugs tend to accumulate in the body. Longer acting secretagogues are to be avoided totally like biguanides. Except linagliptin every gliptin dose has to be reduced in case of moderate to severe RI. Sitagliptin has shown similar reduction of HbA1c in case of moderate/severe RI and in end-stage renal disease (ESRD) patients who are undergoing dialysis compared to glipizide.23 It can also be given after kidney transplant. It has also been shown to reduce albuminuria.21 Saxagliptin dose has to be reduced to half in moderate-severe RI. In RCT, it has been found that after 52 weeks the reduction in HbA1c was greater with saxagliptin than with placebo in the subgroups of patients with moderate and severe RI, but not in the subgroup with ESRD on hemodialysis. In pooled analysis, it has been found that vildagliptin is also safe and effective in case of mild/moderate RI. No dose adjustment is necessary in case of linagliptin. The efficacy (reduction in HbA1c levels) and safety of linagliptin 5 mg was confirmed in T2DM patients with mild or moderate RI in a pooled analysis of three randomized, placebo controlled, Phase III clinical trials, as well as in T2DM patients with severe RI (GFR < 30 mL/min/1.73 m²) in a randomized, double-blind, placebo-controlled trial targeting specifically this population.8

Hepatic Insufficiency

Except vildagliptin, all the gliptins are recommended in case of hepatic insufficiency. Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) often complicate the diabetes mellitus. In Indian diabetic, NAFLD is seen in almost 49% of the patients. Recently in two open label studies, sitagliptin has shown to improve the biochemical parameter as well as the histological feature of NAFLD. It reduces ballooning, NASH score significantly in NAFLD patients.26,27 Linagliptin also has shown promising result in animal model of NAFLD.28

COMBINATION THERAPY

Gliptins can be combined with any antihyperglycemic agents except the GLP-1 analogs. As metformin therapy is considered as the first-line drug in T2DM, most combination trials tested the efficacy and safety of adding a DPP-4 inhibitor to a baseline metformin monotherapy and showed that it was superior to placebo with a mean reduction in HbA1c of 0.6–0.8%.2 Giptins can also be combined with sulfonylurea, pioglitazone (except linagliptin) or insulin. Gliptins can be used as first or second add-on along with these drugs.

SAFETY

Hypoglycemia: The incidence of hypoglycemia is very low. Result of a recent meta-analysis of 39 placebo-controlled trials showed that without concomitant administration of insulin or a sulphonylurea, no elevated risk of hypoglycemia was observed for any gliptins. In contrast, an elevated hypoglycemia risk over placebo was associated with the concomitant administration of linagliptin or sitagliptin and insulin or a sulphonylurea.29

Pancreatitis: The risk of acute pancreatitis with DPP-4 therapy remains a controversial and debated topic. A pooled analysis of controlled clinical trials revealed similar incidence rates of pancreatitis in patients treated with sitagliptin compared with those not treated with sitagliptin (0.08 events per 100 patient-years versus 0.10 events per 100 patient-years, respectively).8

Other adverse effects: The risk of adverse events, serious adverse events and discontinuations due to adverse events is at placebo level for all DPP-4 inhibitors. Overall, DPP-4 inhibitors are not associated with an increased risk of nasopharyngitis (1.06, 0.95–1.19; I² = 0%), upper respiratory tract infection (1.0, 0.83–1.22; I² = 20%) or urinary tract infection (0.86, 0.51–1.45; I² = 64%) compared with any of the hypoglycemic drugs in the control groups.20

PRESENT RECOMMENDATIONS

In the current 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement, DPP-4 inhibitor is recommended as an option for first add on or second add on pharmacological agent. In the previous ADA/EASD consensus statement, recommendation was to start with
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well-validated second-line agents, such as sulfonylureas and basal insulin for patients who are unable to achieve target glucose levels with metformin alone. The higher cost of DPP-4 inhibitors, coupled with an absence of long-term safety and clinical outcome data, was the reason why DPP-4 inhibitors were not selected in the ADA-EASD consensus statement algorithm. But these time DPP-4 inhibitors gained a place in ADA-EASD algorithm (Figure 1). Not only is this, they are also strongly recommended as first add on to metformin in case where minimizing hypoglycemia or avoiding weight gain the main concern.

In the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines, the DPP-4 inhibitors enjoy an exalted position wherein they can be started as either monotherapy or as add on to metformin (Figure 2).

CONCLUSION

The role of DPP-4 inhibitors in the therapeutic armamentarium of T2DM is evolving as their potential strengths and weaknesses become better defined with the passage of time. The core defects of T2DM, viz. progressive \( \beta \)-cell dysfunction, insulin resistance and hepatic glucose overproduction are the areas, which need pharmacological targeting. Moreover T2DM is often accompanied by other conditions (i.e. overweight/obesity with associated metabolic syndrome, high residual CV risk), which are considered as risk factors and thereby, could further affect both morbidity and mortality. DPP-4 inhibitors provide effective and consistent glycemic control. Although they are not more efficacious for reducing HbA\(_1c\) than conventional pharmacological agents but they offer certain advantages like a good tolerability profile, no severe hypoglycemia and no weight gain whatsoever. In addition to stimulating insulin secretion and inhibiting glucagon secretion in a glucose dependent manner, these agents might possibly preserve the \( \beta \) cell mass or function if introduced early in the course of the disease. Together with metformin they can address all the core defect of diabetes. Another potential advantage of DPP-4 inhibitors is their positive effects on CV profile, which might contribute to reduce the incidence of CV events, as suggested by recent meta-analyses. Dipeptidyl peptidase-4 inhibitors are already considered as an important pharmacological class for the management of T2DM, and will probably continue to increase their impact in the near future.

Figure 1: The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) algorithm
Figure 2: The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) algorithm\textsuperscript{31}

REFERENCES

22. Ferreira JCA, Corry D et al. Efficacy and Safety of Sitagliptin versus Glipizide in Patients with Type 2 Diabetes and Moderate to Severe Chronic Renal Insufficiency. ADA poster.
23. Ferreira JCA, Corry D et al. Efficacy and Safety of Sitagliptin vs. Glipizide in Patients with Type 2 Diabetes Mellitus and End-stage Renal Disease on Dialysis.
31. AACE/AACE guidelines: Simplified flowchart for American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2009 glycemic control algorithm.