The Role of Incretin Therapy at Different Stages of Diabetes

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Abstract

The pathogenetic mechanisms causing type 2 diabetes are complex, and include a significant reduction of the incretin effect. In patients with type 2 diabetes, GLP-1 secretion may be impaired, while GIP secretion seems unaffected. In contrast, the insulinotropic activity of GIP is severely altered, whereas that of GLP-1 is maintained to a great extent. Better understanding of the role of incretin hormones in glucose homeostasis has led to the development of incretin-based therapies that complement and offer important advantages over previously used agents. Incretin-based agents have significant glucose-lowering effects, promote weight loss (or are weight-neutral), inhibit glucagon secretion while maintaining counter-regulatory mechanisms, exhibit cardiovascular benefits, and protect β-cells while possessing a low risk profile. At present, incretin-based therapies are most widely used as add on to metformin to provide sufficient glycemic control after metformin failure. However, they are also recommended as monotherapy early in the disease course, and later in triple combination. These agents may also be a promising therapeutic tool in prediabetic subjects. Therefore, a therapeutic algorithm is needed for their optimal application at different stages of diabetes, as suggested in this article.

Keywords: type 2 diabetes · glycemic control · incretin · GLP-1 · DPP-4 · GIP · liraglutide · insulin

Pathophysiological considerations

The core pathophysiological defects leading to type 2 diabetes include increased resistance to insulin action in peripheral tissues and inadequate insulin secretion caused by a progressive decline in β-cell function. It has become apparent that other factors are also involved in the natural history of the disease [1]. Additional mechanisms that further exacerbate the pathological pathways include incretin deficiency and/or resistance, hyperglycemia and increased hepatic sensitivity to glucagon, altered fat metabolism caused by insulin resistance in adipocytes, enhanced glucose reabsorption in the kidneys, and insulin resistance in the central nervous system resulting from neurotransmitter dysfunction [1]. Early in the course of the disease, pancreatic insulin secretion is increased in an attempt to compensate for insulin resistance. Later, β-cells fail to sustain increased secretory rates, which results in gradually declining insulin release and hyperglycemia. Chronically elevated glucose (and lipid) levels cause gluco-lipotoxicity, which in turn further amplifies β-cell failure (by causing de-differentiation of pancreatic β-cells, activation of stress response, accelerated apoptosis, and decreased proliferation) and aggravates insulin resistance (Figure 1) [2].

An important role in the regulation of glucose homeostasis is played by incretins, which are gut-derived hormones released in response to nutrient ingestion (mainly glucose and fat). The two most important hormones found to mediate the "incretin effect" (that is, higher insulin release in response to an oral glucose challenge compared to an
equal intravenous glucose load) are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [3]. These hormones elicit a vast range of effects, including stimulation of insulin secretion in a glucose-dependent manner, and it is estimated that up to 70% of the overall postprandial insulin response to glucose is mediated by them [4, 5].

**Abbreviations:**
- ADA - American Diabetes Association
- BID - twice a day
- BMI - body mass index
- CI - confidence interval
- DPP-4 - dipeptidyl peptidase-4
- EASD - European Association for the Study of Diabetes
- EMA - European Medicines Agency
- FDA - Food and Drug Administration
- GIP - glucose-dependent insulinotropic polypeptide
- GLP-1 - glucagon-like peptide-1
- GLP-1R - GLP-1 receptor
- HbA1c - glycated hemoglobin
- IFG - impaired fasting glucose
- IGT - impaired glucose tolerance
- NEFA - nonesterified fatty acid
- OD - once a day
- TZD - thiazolidinediones

During the development and progression of type 2 diabetes, signals from gut-derived factors are attenuated because of defective release of incretin hormones and/or resistance to their action [6]. The diminished incretin effect is a substantial contributor to insulin deficiency. Combined β-cell dysfunction and incretin deficiency is followed by hyperglycemia, which in turn further amplifies the impairment of incretin secretion and action, in part by downregulating their receptors [2, 7].

The significantly reduced incretin effect has been attributed to decreased secretion. Most of the studies quantifying GIP secretion in subjects with type 2 diabetes have reported that GIP levels are normal or even higher compared with healthy controls [8-10]. However, the insulinotropic effects of GIP have constantly been shown to be attenuated in diabetes, even at supraphysiological levels, implying that secretory defects are not the hallmark of the disease [11-13]. The underlying causes for the impairment of GIP responsiveness in diabetes are not completely understood, but several hypotheses have been proposed, including GIP-receptor mutations, hyperglycemia-associated receptor downregulation/desensitization, post-receptor defects of intracellular machinery, and reduced β-cell function and mass [14-16].

The other defect in the entero-insular axis in type 2 diabetes is related to GLP-1. A number of studies that evaluated GLP-1 secretion levels have indicated similar secretion levels in response to an oral nutrient load in subjects with and without diabetes. However, some reports have shown small reductions in (total and late postmeal) GLP-1 levels, especially in patients with long disease duration and poor metabolic control [8, 17, 18]. In contrast to GIP, the insulinotropic and glucagonostatic activity of GLP-1 is preserved to a high degree in patients with type 2 diabetes. The same applies to its ability to decelerate gastric emptying, although higher levels are needed to maintain physiological activity [12, 19-22]. Several factors, which influence GLP-1 secretory response, have been identified; these include older age, higher weight/BMI, glucagon concentrations, and fasting NEFA [23]. The mechanisms that lead to a glucagon-induced suppression of GLP-1 are still unknown.

To recapitulate, the secretion of GLP-1 is impaired in most patients with diabetes, while the secretion of GIP appears to be unaffected. In contrast, the insulinotropic activity of GIP is severely altered, whereas that of GLP-1 is maintained to a great extent. The two incretins are released independently of each other and have different abilities to stimulate the early- and late-phase insulin secretion which is explained by their distinct intracellular actions: GIP stimulates insulin release from readily available pools in β-cells, while GLP-1 accesses the reserve pools, stimulates insulin biosynthesis, and renders glucose-resistant β-cells more sensitive [9, 22].

Another explanation proposed for the impaired incretin effect is the reduction in overall β-cell function and mass, which occurs during the natural disease history and the defective secretory capacity of β-cells in response to incretin stimuli [6]. Some studies have indicated that the reduction in hyperglycemia partially reverses the impairment of GLP-1 and GIP actions and restores GLP-1 concentrations. This suggests that the diminished incretin effect is rather a consequence of the diabetic state and hyperglycemia, although a genetic component cannot be completely excluded [24].

To explore further the role of incretin release and action dysregulation in the pathophysiology of β-cell failure, studies evaluated GIP/GLP-1 secretion in the pre-diabetic state. The results are inconsistent so far. Some studies indicated modest impairments in GLP-1/GIP secretion, some found increased GIP levels (in association with hyperinsulinemia), and others found no alteration in incretin secretion [25-29]. Thus, while defects in incretin hormone secretion might be present in some
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subjects with impaired glucose tolerance (IGT), both IGT and diabetes can develop in the absence of alterations in incretin secretion. This reinforces the hypothesis that defective incretin release and action in patients with type 2 diabetes is an epiphenomenon of chronic hyperglycemia and not a primary cause [6].

It can thus be concluded that impairment in incretin activity contributes to the deterioration in glucose homeostasis (mainly in the postprandial phase) in patients with diabetes, but is unlikely to predispose to diabetes development.

Incretin-based therapies in the management of type 2 diabetes

With the development of new classes of drugs, treatment options became wider and the management of type 2 diabetes more complex. On the other hand, patients with diabetes have various clinical presentations, different courses of disease, and also different responses to therapeutic agents. When choosing the appropriate therapeutic strategy, several factors should be taken into consideration. Some of these factors are patient-specific (such as age, BMI/waist, duration of diabetes, co-morbidities), some are drug-specific (e.g. mechanisms of action, side effects), while others relate to the disease mechanisms.

Ideally, therapies should address early all pathophysiological disturbances to delay disease progression and to obtain long-lasting metabolic control. Current therapeutic algorithms use oral agents in a stepwise, additive manner when specific targets are not reached. This approach, however, does not prevent β-cell loss, nor does it assure sustainable glycemic control, and ultimately it leads to treatment failure [1, 30]. Also, the use of available agents is often impeded by their adverse effects (mainly hypoglycemia, weight gain, and edema) and/or the inability to meet certain requirements (such as optimal control of postprandial hyperglycemia) [30-32] (Table 1).

Therefore, new drugs have been developed that target the core abnormalities of diabetes and have minimal side effects. A better understanding of the role of incretin hormones in maintaining glucose homeostasis has led to the development of two groups of incretin-based therapies: 1. GLP-1 receptor (GLP-1R) agonists, which are degradation-resistant synthetic/chemically-modified peptides that bind GLP-1 receptors and mimic the action of naturally occurring GLP-1 (incretin mimetics), and 2. dipeptidyl peptidase 4 (DPP-4) inhibitors, which, by inhibiting the enzyme, decrease the degradation of endogenous incretin hormones (both GLP-1 and GIP), and thus prolong their activity (incretin enhancers) [22].

The biological effects of incretins or incretin-based therapies have been reviewed in detail elsewhere [33, 34]. At the pancreatic level, incretins have pleiotropic actions. After binding to specific receptors on β-cells incretins promote the following effects:
1. Insulin gene transcription, biosynthesis, and determination of a glucose-dependent stimulation of insulin secretion (in conjunction with reduction of plasma glucagon and delayed gastric emptying, this results in a glucose-lowering effect).
2. β-cell survival and possibly β-cell proliferation/neogenesis.
4. Improvement of β-cell responsiveness to glucose (possibly through upregulation of the biosynthesis of other β-cell products such as glucokinase and glucose transporters) [38].

Furthermore, GLP-1/GLP-1R agonists shift the dynamics of insulin secretion towards an earlier response and restore the biphasic profile [39].

In addition, a number of extrapancreatic actions have been described, some contributing to the glucoregulatory effects [40]. Incretins regulate feeding behavior by enhancing satiety/suppressing Table 1. Possible treatment algorithm for type 2 diabetes therapy at various stages

<table>
<thead>
<tr>
<th>Stage of diabetes</th>
<th>Suggested intervention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes (IFG, IGT)</td>
<td>Lifestyle optimization (LSO) Pharmacologic intervention (not yet approved for prediabetes): metformin (incretin-based therapies might also be beneficial)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>double therapy</td>
<td>LSO + metformin + SU/TZD/DPP-4 inhibitors/GLP-1R agonists/insulin</td>
<td>- Metformin + SU: long-term clinical experience, different mechanisms of action. - Metformin + TZD: preferable when insulin resistance is important. - Metformin + DPP-4 inhibitors / GLP-1R agonists: different mechanisms of action, weight control, low risk hypoglycemia. - DPP-4 inhibitors / GLP-1R agonists + SU: higher risk of hypoglycemia (SU dose may be decreased). - DPP-4 inhibitors / GLP-1R agonists + TZD: preferable when insulin resistance is a problem and metformin is contraindicated/ not tolerated. - Insulin: sitagliptin is approved for use in double combination with insulin.</td>
</tr>
<tr>
<td>triple therapy</td>
<td>LSO + metformin + TZD + SU/DPP-4 inhibitors/GLP-1R agonists/insulin</td>
<td>M etformin + TZD + SU/DPP-4 inhibitors/GLP-1R agonists: preferable when insulin resistance is important (in combination with DPP-4 inhibitors/GLP-1R agonists: low risk of hypoglycemia).</td>
</tr>
<tr>
<td></td>
<td>LSO + metformin + SU + DPP-4 inhibitors/GLP-1R agonists/insulin</td>
<td>M etformin + SU + DPP-4 inhibitors/GLP-1R agonists: may be considered when insulin secretion deficit is important, higher risk of hypoglycemia (SU dose may be decreased).</td>
</tr>
</tbody>
</table>

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Incretin Therapy in Prediabetes: Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

Evidence exists that the period between the earliest abnormalities of glucose metabolism and the onset of diabetes is long and that a high proportion of individuals with prediabetes are likely to progress to diabetes or to remain in the abnormal glycemic state [46]. Therefore, various intervention strategies to prevent progression to overt disease have been sought. Questions have been raised whether these interventions, even if effective, truly prevent or just delay the disease. A definite answer would require long-term follow-up studies, but even in the second situation, a potential benefit could be envisaged, given the fact that lifetime exposure to higher glycemic concentrations is shortened, and thus diabetes-related morbidity deferred [47].

Well-designed preventive trials have demonstrated that lifestyle modification and pharmacologic interventions that target hyperglycemia are effective in reducing the occurrence of diabetes in at-risk individuals [48-58]. Several clinical trials have indicated that intensive lifestyle interventions provide the greatest decrease in the incidence of diabetes [48-50]. Pharmacological agents (metformin, thiazolidinediones (TZD), acarbose, nateglinide, orlistat, ramipril, and valsartan) have been evaluated for the prevention of diabetes and cardiovascular disease in patients with IFG/IGT and some of them have been associated with slower progression to diabetes [51-58]. However, there are many issues (including cost-effectiveness) that need to be considered before medications are recommended for preventive purposes. The American Diabetes Association (ADA) consensus statement indicates that metformin is the only oral agent that should be used in subjects having IFG, IGT, and an additional risk factor [46]. However, the use of medication in IFG/IGT is not yet approved by regulatory agencies.

Evidence for the efficacy of incretin-based therapy in the prediabetic stage is minor. Some data suggest that obese individuals with IFG or IGT treated with exenatide along with lifestyle interventions for 24 weeks reverted to normal glucose tolerance [59]. In individuals with IFG, therapy with vildagliptin improved postprandial glucose levels after 6 weeks, but the effect was not maintained beyond the wash-out period, possibly because of the short duration of treatment [60]. Similarly, an eight-week treatment with sitagliptin did not change fasting or postprandial glucose levels in subjects with IFG, but again, it is not clear whether the duration of therapy was long enough for the effects to occur [61]. A twelve-week study, however, reported that IGT subjects treated with vildagliptin presented a decrease in peak and total glycemic excursions [62]. Thus, limited evidence regarding incretin-based therapy in prediabetes seems to point to some benefit, but it appears that the treatment needs to be of long duration. It is hypothesized that these agents might be used to prevent or delay the progression to overt diabetes, but long-term, large clinical trials are needed to evaluate this potential. It is however necessary to demonstrate first that incretin-based therapies improve glucose homeostasis (and maybe also β-cell function/mass) in prediabetic individuals.

Incretin Therapy in the Early Stages of Type 2 Diabetes (Monotherapy)

Current ADA, EASD, and other association guidelines for the management of type 2 diabetes advocate initiating lifestyle changes (to decrease weight and increase physical activity) and metformin early after diagnosis to achieve glycemic goals [31, 63-65]. Metformin is the preferred first therapy for most patients, barring contraindications, because of the extensive clinical experience available, its beneficial safety profile, and its cost-effectiveness. Recent data indicate that metformin also modulates components of the incretin axis; it increases GLP-1 concentration by enhancing pre-
proglucagon expression, and increases expression of the GLP-1 receptor [66, 67].

However, the choice of the glucose-lowering drug should be individualized, and specific patient characteristics, problems, and disease-specific factors should also be taken into account, beside those related to the drug itself. When considering drugs, not only the glucose-lowering effects should be taken into account, but also other advantages and disadvantages should be considered within the limits of approved indications (Table 1) [32, 68].

Because of limited study data and clinical experience, guidelines currently do not recommend incretin-based therapies as first option for monotherapy in newly diagnosed diabetes. However, in certain situations (e.g. when metformin is contraindicated or not tolerated, and when hypoglycemia or weight gain constitute a problem), they should be considered as a treatment option. GLP-1R agonists have certain advantages such as low risk of hypoglycemia, favorable weight effects allowing weight loss, potential cardiovascular benefits, and protective effects on β-cells. They also have proven efficacy in terms of reducing fasting and postprandial glucose concentration and glycated hemoglobin (HbA1c) [69, 70]. A recent meta-analysis indicated that compared with placebo, patients showed the following overall reductions in HbA1c when treated with different agents [70]:

1. Liraglutide -1.03% (95% CI: -1.16 to -0.90, p < 0.001).
2. Exenatide -0.75% (95% CI: -0.83 to -0.67, p < 0.001).
3. Sitagliptin -0.79% (95% CI: -0.93 to -0.65, p < 0.001).
4. Vildagliptin -0.67% (95% CI: -0.83 to -0.52, p < 0.001).

Another meta-analysis combined data from randomized controlled trials (with at least a 12-week duration) that used a GLP-1R agonist or a DPP-4 inhibitor. It showed that a higher propor-

Table 2. Summary of efficacy data in randomized controlled trials with GLP-1R agonists

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study term (wk)</th>
<th>Diabetes duration (yr)</th>
<th>HbA1c decrease (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide 5µg/ 10µg BID</td>
<td>24</td>
<td>2(±3)</td>
<td>-0.7(±0.1)/-0.9(±0.1)</td>
<td>Moretto TJ, et al. 2008[71]</td>
</tr>
<tr>
<td>Exenatide 2.5µg/ 5µg/ 7.5µg/ 10µg</td>
<td>4</td>
<td>4.5(±5)/2.9(±2.5)/3.8(±6.6)</td>
<td>-0.3(±0.1)/-0.4(±0.1)/-0.5(±0.1)</td>
<td>Poon T, et al. 2005 [72]</td>
</tr>
<tr>
<td>Liraglutide 0.1mg/ 0.3mg/ 0.6mg/ 0.9mg</td>
<td>14</td>
<td>7.48(±5.6)</td>
<td>-0.79(±1.08,±0.50)/-1.22(±1.50,±0.93)/-1.64(±1.93,±1.35)/-1.85(±2.14,±1.56)</td>
<td>Seino T, et al. 2008 [73]</td>
</tr>
<tr>
<td>Liraglutide 1.9mg/ 1.25mg/ 0.65mg</td>
<td>14</td>
<td>4(1-29)</td>
<td>-1.45/-1.40/-0.98</td>
<td>Vilsbøll T, et al. 2007 [74]</td>
</tr>
<tr>
<td>Liraglutide 1.2mg/ 1.8mg</td>
<td>52</td>
<td>5.2(±5.5)/5.3(±5.1)</td>
<td>-0.84(±0.23)/-1.14(±0.24)</td>
<td>Garber A, et al. 2009 [75]</td>
</tr>
<tr>
<td>Combination therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide 5µg/ 10µg BID + metformin</td>
<td>26</td>
<td>6.2(±5.9)/4.9(±4.7)</td>
<td>-0.40(±0.11)/-0.78(±0.10)</td>
<td>DeFronzo RA, et al. 2005 [93]</td>
</tr>
<tr>
<td>Exenatide 5µg/ 10µg BID + sulfonylurea</td>
<td>30</td>
<td>6.3(±5.2)/6.6(±6.6)</td>
<td>-0.46(±0.12)/-0.86(±0.11)</td>
<td>Buse JB, et al. 2004 [95]</td>
</tr>
<tr>
<td>Exenatide 10µg BID + thiazolidindione</td>
<td>16</td>
<td>7.3(±4.9)</td>
<td>-0.89</td>
<td>Zinman B, et al. 2007 [97]</td>
</tr>
<tr>
<td>Liraglutide 0.6mg/ 1.2mg/ 1.8mg + metformin</td>
<td>26</td>
<td>7(±5)/7(±5)/8(±5)</td>
<td>-0.8(-1.0,-0.6)/-1.1(-1.3,-0.9)/-1.1(-1.3,-0.9)</td>
<td>Nauck M, et al. 2009 [94]</td>
</tr>
<tr>
<td>Liraglutide 0.6mg/ 1.2mg/ 1.8mg + sulfonylurea</td>
<td>26</td>
<td>6.5(4.0,10.2)/6.7(4.0,10.7)/6.5(3.7,10.5)</td>
<td>-0.6/-1.08/-1.13</td>
<td>Marre M, et al. 2009 [96]</td>
</tr>
</tbody>
</table>

Legend: Data for diabetes duration are mean ±SD. BID: twice daily. * Odds ratio and 95% CI.
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Table 3. Summary of efficacy data in randomized controlled trials with DPP-4 inhibitors monotherapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study term (wk)</th>
<th>Diabetes duration (yr)</th>
<th>HbA1c decrease (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100mg/200mg QD</td>
<td>24</td>
<td>4.3±4.9/4.3±4.7</td>
<td>-0.61(-0.74,-0.49)/-0.76(-0.88,-0.64)</td>
<td>Ashner P, et al. 2006 [76]</td>
</tr>
<tr>
<td>Sitagliptin 25mg/50mg/100mg QD/50mg BID</td>
<td>12</td>
<td>3.6±3.4/3.3±3.9/3.6±3.9/4.5±5.9</td>
<td>-0.28(-0.42,-0.14)/-0.44(-0.58,-0.30)/-0.43(-0.56,-0.29)</td>
<td>Hanefeld M, et al. 2007 [77]</td>
</tr>
<tr>
<td>Sitagliptin 100mg</td>
<td>18</td>
<td>2.1±1.7</td>
<td>-0.7(-0.8,-0.6)</td>
<td>Mohan V, et al. 2009 [78]</td>
</tr>
<tr>
<td>Sitagliptin 100mg BID</td>
<td>12</td>
<td>4.0±4.1</td>
<td>-0.65(-0.80,-0.50)</td>
<td>Nonaka K, et al. 2008 [79]</td>
</tr>
<tr>
<td>Sitagliptin 5mg/12.5mg/25mg/50mg BID</td>
<td>12</td>
<td>4.3±4.1/4.9±5.0/5.0±5.2/4.2±4.0</td>
<td>-0.15(-0.29,-0.01)/-0.41(-0.55,-0.27)/-0.43(-0.56,-0.29)/-0.54(-0.68,-0.40)</td>
<td>Scott R, et al. 2007 [80]</td>
</tr>
<tr>
<td>Sitagliptin 100mg/200mg QD</td>
<td>18</td>
<td>4.5±4.3/4.5±3.9</td>
<td>-0.48(-0.61,-0.35)/-0.36(-0.48,-0.23)</td>
<td>Raz I, et al. 2006 [81]</td>
</tr>
<tr>
<td>Vildagliptin 25mg BID/25mg/50mg/100mg QD</td>
<td>12</td>
<td>3.2±3.8/3.1±5.1/2.7±3.2/3.0±2.7</td>
<td>-0.31(-0.41,-0.27)/-0.56(-0.33,-0.21)</td>
<td>Ristic S, et al. 2005 [82]</td>
</tr>
<tr>
<td>Vildagliptin 50mg QD/50mg BID/100mg QD</td>
<td>24</td>
<td>2.1±3.6/2.1±3.3/2.4±2.2</td>
<td>-0.8(-0.1)/-0.8(-0.1)/-0.9(-0.1)</td>
<td>Dejager S, et al. 2007 [83]</td>
</tr>
<tr>
<td>Vildagliptin 10mg/25mg/50mg BID</td>
<td>12</td>
<td>4.5±4.2/4.7±4.5/4.7±4.3</td>
<td>-0.53(-0.67,-0.92)</td>
<td>Kikuchi M, et al. 2009 [84]</td>
</tr>
<tr>
<td>Vildagliptin 50mg QD/50mg BID/100mg QD</td>
<td>24</td>
<td>1.8±2.7/2.4±3.2/2.1±2.9</td>
<td>-0.5(-0.1)/-0.7(-0.1)/-0.8(-0.1)</td>
<td>Pi-Sunyer FX, et al. 2007 [85]</td>
</tr>
<tr>
<td>Vildagliptin 50mg</td>
<td>52+52</td>
<td>2.1±2.1</td>
<td>-0.3±0.1/0.5±0.2</td>
<td>Scherbaum WA, et al. 2008 [86]</td>
</tr>
<tr>
<td>Vildagliptin 100mg</td>
<td>52</td>
<td>1</td>
<td>-1.0±0.1</td>
<td>Schweizer A, et al. 2007 [87]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg/10mg</td>
<td>24</td>
<td>3.1±3.5/2.5±3.3/2.3±3.1</td>
<td>-0.43(-0.46,-0.54)</td>
<td>Rosenstock J, et al. 2009 [87]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg/10mg/20mg/40mg/100mg QD</td>
<td>12</td>
<td>1.0±0.0-14.0/0.8(0.0-8.2)/0.7(0.0-12.9)/1.7(0.0-13)/1.3(0.0-19)/0.5(0.0-26)</td>
<td>-0.72(-0.12,-0.90(-0.14)/-0.81(-0.11,-0.74)/-0.80(-0.12,-1.09(-0.09))</td>
<td>Rosenstock J, et al. 2008 [88]</td>
</tr>
</tbody>
</table>

Legend: Data for diabetes duration are mean ± SD. BID: twice daily. QD: once daily. *Odds ratio and 95% CI.

Summary of efficacy data in randomized controlled trials with DPP-4 inhibitors monotherapy achieved target goals of HbA1c < 7.0% compared to placebo/standard treatment groups at the end of the study period [69]. Table 2 summarizes the efficacy data in clinical trials that evaluated GLP-1R agonists and Tables 3 and 4 the data on DPP-4 inhibitors in monotherapy and combination therapy.

Data from clinical trials indicate that, when used as monotherapy, exenatide 5 µg/10 µg BID showed a significant reduction in mean HbA1c compared with placebo (in the range of -0.4% to -0.9%), while various doses of liraglutide (from 0.1 to 1.9 mg QD) caused a dose-dependent decrease in HbA1c ranging from -0.79% to -1.85% [71-74]. In comparison to a sulfonylurea (i.e. glimepiride), 1.2 mg/1.8 mg of liraglutide in monotherapy significantly lowered mean HbA1c by 0.84%/1.14% [75].

Even more clinical studies evaluated the effect of DPP-4 inhibitors as single therapeutic agents on glycemic control. Various doses of sitagliptin (starting from 5 mg BID to 200 mg QD), given in subjects not controlled by lifestyle interventions alone, determined a dose-dependent decrease in HbA1c ranging from -0.15% to -0.76% [76-81]. Sitagliptin 100 mg QD (the regimen used in clinical practice) lowered mean HbA1c by 0.44% to 0.7% [75-78, 80]. Monotherapy with vildagliptin in

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doses evaluated in clinical trials ranging from 10 mg BID to 100 mg QD achieved a 0.2% to 0.92% reduction in HbA1c versus placebo at study end [82-86]. Intervention with saxagliptin as monotherapy at different doses (2.5 mg to 100 mg) was associated with a significant decrease in HbA1c ranging from -0.43% to -1.09% compared with placebo [87, 88]. Compared with metformin, 100 mg vildagliptin in monotherapy significantly reduced mean HbA1c by 1.0% from baseline, but statistical non-inferiority to metformin 1000 mg twice daily has not been demonstrated [89].

At present, only sitagliptin (100 mg QD) is approved for use as monotherapy by both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). Exenatide (5 µg/10 µg BID) and saxagliptin (2.5 mg/5 mg QD) are approved as monotherapy only by the FDA. Vil-

**Table 4. Summary of efficacy data in randomized controlled trials with DPP-4 inhibitors combination therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study term (wk)</th>
<th>Diabetes duration (yr)</th>
<th>HbA1c decrease (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100mg + metformin</td>
<td>24</td>
<td>4.9(±0.2)-19.0</td>
<td>-0.73(-0.87, -0.60)</td>
<td>Scott R, et al. 2008 [98]</td>
</tr>
<tr>
<td>Sitagliptin 100mg + metformin</td>
<td>24</td>
<td>6.0(±0.5)</td>
<td>-0.67(-0.77, -0.57)</td>
<td>Charbonnel B, et al. 2007 [99]</td>
</tr>
<tr>
<td>Sitagliptin 50mg BID + metformin</td>
<td>24</td>
<td>4.5(±0.7)/4.4(±4.2)</td>
<td>-1.40(-1.56, -1.24)/-1.90(-2.06, -1.74)</td>
<td>Goldstein BJ, et al. 2007 [100]</td>
</tr>
<tr>
<td>Sitagliptin 100mg + metformin</td>
<td>30</td>
<td>8.4(±6.5)</td>
<td>-1.0(-1.3, -0.7)</td>
<td>Raz I, et al. 2008 [101]</td>
</tr>
<tr>
<td>Sitagliptin 100mg + sulfonylurea</td>
<td>24</td>
<td>8.3(±5.5)</td>
<td>-0.45(-0.57, -0.34)</td>
<td>Hermansen K, et al. 2007 [108]</td>
</tr>
<tr>
<td>Sitagliptin + thiazolidindione</td>
<td>24</td>
<td>6.1(±5.4)</td>
<td>-0.85(-0.98, -0.72)</td>
<td>Rosenstock J, et al. 2006 [111]</td>
</tr>
<tr>
<td>Sitagliptin + insulin</td>
<td>24</td>
<td>13(±7)</td>
<td>-0.6(-0.7, -0.5)</td>
<td>Lind Y, et al. 2010 [116]</td>
</tr>
<tr>
<td>Vildagliptin 50mg + metformin</td>
<td>52</td>
<td>5.8(±4.2)</td>
<td>-0.6(±0.1)</td>
<td>Ahren B, et al. 2004 [102]</td>
</tr>
<tr>
<td>Vildagliptin 50mg/100mg + metformin</td>
<td>24</td>
<td>6.8(±5.5)/6.8(±4.7)</td>
<td>-0.7(±0.1)/-1.1(±0.1)</td>
<td>Bosi E, et al. 2007 [103]</td>
</tr>
<tr>
<td>Vildagliptin 100mg + metformin</td>
<td>24</td>
<td>6.1(±5.4)</td>
<td>-0.85(-0.98, -0.72)</td>
<td>Goodman M, et al. 2009 [104]</td>
</tr>
<tr>
<td>Vildagliptin 50mg BID + metformin</td>
<td>52</td>
<td>5.71(±5.18)</td>
<td>-0.44(-0.47, -0.41)</td>
<td>Ferrarini E, et al. 2008 [105]</td>
</tr>
<tr>
<td>Vildagliptin 50mg/100mg + sulfonylurea</td>
<td>24</td>
<td>6.9(±5.2)/6.7(±5.3)</td>
<td>-0.58(±0.10)/-0.63(±0.09)</td>
<td>Garber AJ, et al. 2008 [109]</td>
</tr>
<tr>
<td>Vildagliptin 50mg/100mg + thiazolidindione</td>
<td>24</td>
<td>4.7(±4.3)/4.6(±4.8)</td>
<td>-0.8(±0.1)/-1.0(±0.1)</td>
<td>Garber AJ, et al. 2007 [112]</td>
</tr>
<tr>
<td>Vildagliptin + insulin</td>
<td>24</td>
<td>14.4(±6.6)</td>
<td>-0.5(±0.1)</td>
<td>Fonseca V, et al. 2007 [115]</td>
</tr>
<tr>
<td>Saxagliptin 5mg/10mg + metformin</td>
<td>24</td>
<td>2.0(±3.6)/1.4(±2.5)</td>
<td>-2.5/-2.5</td>
<td>Jazdinsky M, et al. 2009 [106]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg/10mg + metformin</td>
<td>24</td>
<td>6.7(±5.6)/6.4(±4.7)/6.3(±4.4)</td>
<td>-0.59(±0.07)/-0.69(±0.07)/-0.58(±0.07)</td>
<td>DeFronzo RA, et al. 2009 [107]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg + sulfonylurea</td>
<td>24</td>
<td>7.1(±5.9)/6.8(±5.8)</td>
<td>-0.54/-0.64</td>
<td>Chacra AR, et al. 2009 [110]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg + thiazolidindione</td>
<td>24</td>
<td>5.3(±4.6)/5.2(±5.6)</td>
<td>-0.66/-0.94</td>
<td>Hollander P, et al. 2009 [113]</td>
</tr>
<tr>
<td>Saxagliptin 2.5mg/5mg + thiazolidindione</td>
<td>72 (24+48)</td>
<td>5.3(±4.6)/5.2(±5.6)</td>
<td>-0.59(-0.75, -0.43)/-1.09(-1.26, -0.93)</td>
<td>Hollander P, et al. 2011 [114]</td>
</tr>
</tbody>
</table>

**Legend:** Data for diabetes duration are mean ± SD. BID: twice daily. QD: once daily. *Odds ratio and 95% CI. **Mean ± SE.
Incretin therapy in more advanced stages of type 2 diabetes (double or triple combination)

In the second step, treatment intensification with incretin mimetics and DPP-4 inhibitors is appropriate when one drug alone is not sufficient to achieve glycemic goals. Basically, there are four options, namely adding incretin mimetics to i) metformin, ii) pioglitazone (the only available drug of the TZD class at present), iii) a sulfonylurea, or iv) insulin.

When used in association with metformin or pioglitazone, the main advantages of incretins are pathophysiological. These two drugs are insulin sensitizers (in liver, muscle, and adipose tissues in the case of TZDs), while incretins target different pathological mechanisms (as discussed above), and thus potentiate the glucose-lowering action.

When combined with metformin, the key benefits of incretins are avoidance of hypoglycemia and better weight control. The addition of DPP-4 inhibitors or incretin mimetics to metformin is of particular benefit in patients who need an increase in endogenous insulin secretion, but who would be at high risk for hypoglycemia from sulfonylureas. Both incretins and TZDs are supposed to have beneficial effects on β-cells by preserving and improving their function and possibly increasing β-cell mass [90]. Some data suggest that metformin has a protective effect on β-cells (indirectly by ameliorating gluco- and lipotoxicity), but a direct positive effect of metformin on β-cells is not generally accepted [90].

Sulfonylureas have been associated with a progressive decline in β-cell function and a concomitant loss of glycemic control [1, 90]. Sulfonylureas are more problematic when used in combination with incretins because of the possible occurrence of glucose-independent stimulation of insulin secretion that increases the risk of hypoglycemia [91, 92]. Hypoglycemic episodes can be minimized by reducing the sulfonylurea dose on incretin initiation, but this approach may also decrease treatment effectiveness.

The complementary effect of incretin-based therapies and insulin on fasting and postprandial glucose control provides a rationale for association of these agents in the management of type 2 diabetes.

In clinical trials, exenatide 5 µg (10 µg) BID in association with metformin decreased mean HbA1c by 0.4% (0.8%), while liraglutide induced a decrease of 0.7% to 1.0% (for doses ranging from 0.6 mg to 1.8 mg) [93, 94]. In combination with a sulphonylurea, the mean HbA1c change was -0.46% (-0.86%) for 5 µg (10 µg) of exenatide BID, and -0.6% to -1.1% for doses ranging from 0.6 mg to 1.8 mg of liraglutide [95, 96]. Mean HbA1c was reduced by 0.89% when 10 µg BID exenatide was added to a thiazolidindione (± metformin) [97].

Several studies evaluated the effect on HbA1c when sitagliptin was added to metformin. They showed a decrease of 0.66% to 1.9% [98-101]. Vildagliptin in combination with metformin reduced mean HbA1c by 0.44%-0.9%, while saxagliptin combined with metformin caused a decrease of 0.58% to 2.5% (for doses between 2.5 mg and 10 mg) [102-107]. In association with a sulfonylurea, sitagliptin 100 mg decreased HbA1c by 0.3%, vildagliptin 50 mg (100 mg) by 0.58% (0.63%), and saxagliptin by 0.54%-0.64% [108-110]. Clinical studies indicated that, in association with pioglitazone, sitagliptin 100 mg lowered HbA1c by 0.85%, vildagliptin 50 mg (100 mg) by 0.8% (1.0%),

Table 5. Clinical characteristics of GLP-1 receptor agonists and DPP-4 inhibitors [33, 66, 124]

<table>
<thead>
<tr>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous injection therapy</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Reduces appetite/ delays gastric emptying</td>
<td>Influences appetite/ gastric emptying</td>
</tr>
<tr>
<td>Weight reduction (significant and sustained)</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>HbA1c reduction (by -0.75%±1.03%)</td>
<td>HbA1c reduction (by -0.67%-0.79%)</td>
</tr>
<tr>
<td>Fasting and postprandial glycemia reduction (slightly more)</td>
<td>Fasting and postprandial glycemia reduction (slightly less)</td>
</tr>
<tr>
<td>Improvements in blood pressure, lipids, and amino transferases</td>
<td>Some improvements in lipids (or no significant effects)</td>
</tr>
<tr>
<td>Side effects: gastrointestinal (mostly nausea); possible link to pancreatitis; low risk of hypoglycemia</td>
<td>Side effects: infections; headache; possible link to pancreatitis; low risk of hypoglycemia</td>
</tr>
</tbody>
</table>

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and saxagliptin 2.5 mg (5 mg) combined with a TZD by 0.59% (1.09%) [111-114]. Combination of vildagliptin with insulin (intermediate- or long-acting insulin plus prandial insulin) yielded a significant reduction in HbA1c (-0.5%) compared with placebo [115]. Similarly, the addition of sitagliptin to ongoing insulin therapy (with or without metformin) significantly reduced HbA1c by 0.6% from baseline compared with placebo, regardless of the type of insulin (long-acting, intermediate acting or premixed) [116].

Liraglutide is approved for use in association with metformin or a sulfonylurea, exenatide, vildagliptin, and saxagliptin in combination with metformin or a sulfonylurea or TZD. Sitagliptin can be used with metformin, a sulfonylurea, TZD or insulin. Currently, there are combinations of drugs available (vildagliptin + metformin approved by the EMA, saxagliptin + metformin approved by the FDA, and sitagliptin + metformin approved by both agencies), which have the potential to increase treatment compliance.

At the third stage of treatment intensification, a triple drug combination may be considered for patients that do not achieve adequate glycemic control on double therapy, and when insulin treatment is not the preferred choice. At this stage, the best alternative could be to associate incretin-based agents with metformin and a TZD, especially when insulin resistance is the main concern. Exenatide, liraglutide, and sitagliptin are approved for use in triple combination with metformin and sulfonylurea/TZD.

In clinical studies, when GLP-1R agonists were used in triple therapy (with TZD plus metformin or with a sulphonylurea plus metformin) HbA1c decreased by 0.55%-1.5% [117-121]. A similar decrease (-0.89%) was observed for sitagliptin in combination with two other oral agents (metformin plus sulphonylurea) versus placebo [108]. Several studies tested incretin mimetics against insulin. They found that exenatide provided similar glycemic control, and liraglutide was slightly superior to insulin glargine in terms of HbA1c reduction [118-120, 122-125]. The treatment with GLP-1R agonists was associated with significant weight loss, and there was no significant difference between treatment groups in the incidence of hypoglycemic episodes [118-120, 122-125]. However, one study, including subjects in a more advanced stage of diabetes (with high HbA1c values at baseline and a long duration of diabetes), reported that significantly more patients achieved glycemic goals when treated with premixed insulin than with exenatide [126]. This implies that incretin-based therapy should be initiated at a stage when there is sufficient β-cell function for the drugs to be effective. Therefore, at the third stage of therapy intensification, various factors should be considered to decide whether insulin initiation or triple therapy would be the best choice.

**GLP-1R agonists or DPP-4 inhibitors?**

Several aspects, apart from their mechanism of action, distinguish the two drug classes, GLP-1R agonists and DPP-4 inhibitors (Table 5). These aspects might help clinicians to identify which patients benefit most from intervention with a drug from which class. The main differences are:

1. GLP-1R agonists are given by subcutaneous injection, while DPP-4 inhibitors are administered as oral tablets. In certain situations, the route of administration might be of significance, as regarding the convenience of use and adherence.
2. GLP-1R agonists are associated with significant and sustained weight loss, while DPP-4 inhibitors tend to be weight-neutral.
3. Therapy with GLP-1R agonists is associated with higher incidence of adverse gastrointestinal effects, particularly nausea, while infections seem to be more frequent with DPP-4 inhibitors.
4. GLP-1R agonists are generally associated with a slightly more robust glucose-lowering efficacy, as the mean HbA1c reductions are more pronounced (0.75%-1.03% with GLP-1R agonists compared to 0.67%-0.79% with DPP-4 inhibitors) [70]. Studies that directly compared exenatide or liraglutide with sitagliptin supported this assumption by demonstrating greater lowering of mean HbA1c (mean treatment differences for 1.8 mg (1.2 mg) liraglutide versus 100 mg sitagliptin were -0.60% (-0.34%), and -0.6% for 2 mg exenatide LAR versus 100 mg sitagliptin) [125, 126]. Also, some studies have shown that exenatide lowered 2-hour postprandial glucose levels more effectively, and caused significantly lower average 24-hour glucose, than sitagliptin [127, 128].
The differences between incretin mimetics and incretin enhancers may be explained, at least in part, by higher circulating levels of the active agents obtained with GLP-1R agonists and possibly stronger receptor stimulation. Lower concentrations of endogenous GLP-1 are achieved after DPP-4 inhibition. Because of the progressive loss of GLP-1 secretion at more advanced stages of diabetes, it has been suggested that a replacement therapy using GLP-1R agonists is preferable over DPP-4 inhibitor treatment. DPP-4 inhibitors may not sufficiently lower blood glucose at later stages because diminished GLP-1 secretion [129-131]. However, studies that included patients with longer duration of diabetes treated with an incretin enhancer have shown efficacy in controlling blood glucose. On the other hand, there are no long-term longitudinal studies available at present that follow up the pattern of GLP-1 secretion during the natural history of the disease, and define the time-point and markers predicting the lack of response to DPP-4 inhibitors [23].

Conclusions and future directions

Incretin-based therapy complements and brings important and unique advantages to the therapeutic spectrum for type 2 diabetes. It addresses underlying pathophysiological abnormalities associated with the disease that are not targeted by other drugs, and has significant glucose-lowering and extraglycemic effects. There seems to be a consensus that a treatment algorithm based on pathophysiology is desirable. Thus, selecting (a combination of) drugs from classes that target various disease mechanisms would provide durable results in terms of metabolic control and would benefit β-cell function [1, 32]. Therefore, an early association between metformin ± pioglitazone (which increase insulin sensitivity, reduce hepatic glucose production (both drugs), inhibit lipolysis, and protect β-cells (TZD)) with an insulinotropic agent is reasonable.

A combination of sulfonylureas and DPP-4 inhibitors (or GLP-1R agonists) is beneficial early in the course of the disease. This is because sulfonylureas are associated with the progressive loss of metabolic control (after an initial decrease of HbA1C), which is due to the progressive loss of β-cells associated with their use. The combination with DPP-4 inhibitors (and GLP-1R agonists) would aid by improving β-cell function and maintain durability of glycemic control. Another benefit of adding incretin-based therapies is that they stimulate insulin secretion in a glucose-dependent manner. Therefore, they are associated with less hypoglycemia and weight gain than sulfonylureas. Finally, incretins target an additional pathological mechanism (hyperglucagonemia), in contrast to sulfonylureas. Therefore, even if these drugs are more expensive than sulfonylureas, it is easy to conclude that, in the future, incretin-based therapies should be used as insulinotropic agents on a larger scale and early in the disease course, because of their numerous advantages over sulfonylureas.

However, several points related to therapy with an incretin mimetic/enhancer still need to be evaluated and clarified:

1. When is the best moment to start incretin-based therapies, in the early or later stages of the disease? At present, these drugs are most likely to be used in addition to metformin, when monotherapy does not provide sufficient glycemic control. However, data from preclinical studies, indicating favorable effects on β-cell function, suggest that early intervention is more beneficial, but this needs to be proven by clinical trials. If the protective effect on β-cell health is assured, which might have disease-modifying potential by delaying the onset or slowing the progression of diabetes, then the current therapeutic algorithm may undergo changes.

2. Which drug (GLP-1R agonist or DPP-4 inhibitor) should be used at which stage? According to some suggestions, it is better to use DPP-4 inhibitors at an earlier stage of disease (when there is enough endogenous incretin secretion), while at later stages, a replacement therapy (with a GLP-1R agonist) is more efficient. However, this hypothesis needs validation by well-designed clinical trials.

3. Is there any marker that could predict a positive response to therapy? Identification of such markers would help to define the specific patient profiles that would be most likely to benefit from the therapy. It would also help to address patients’ needs more appropriately.

4. What is the impact of incretin-based therapy on long-term glycemic exposure and diabetic complications? Studies that could prove definite positive clinical outcomes (i.e. prevention or even improvement of
chronic complications) will certainly help to improve diabetes management strategies.

There is evidence that not all patients with type 2 diabetes benefit equally from current treatment guidelines. Answers to the abovementioned and other questions will be helpful to characterize an efficient and individualized therapeutic approach for improving care.

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