Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes: An Updated Review and Challenging Clinical Scenarios

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REVIEW

Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes: An Updated Review and Challenging Clinical Scenarios

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ABSTRACT

The safety and efficacy of dipeptidyl peptidase-4 (DPP4) inhibitors as monotherapy or in combination with other oral antidiabetic agents or basal insulin are well established. DPP4 inhibitors stimulate glucose-dependent insulin secretion and inhibit glucagon production. As monotherapy, they reduce the hemoglobin A1c level by about 0.6–0.8%. The addition of a DPP4 inhibitor to basal insulin is an attractive option, because they lower both postprandial and fasting plasma glucose concentrations without increasing the risk of hypoglycemia or weight gain. The present review summarizes the extensive evidence on the combination therapy of DPP4 inhibitors and insulin-based regimens in patients with type 2 diabetes. We focus our discussion on challenging clinical scenarios including patients with chronic renal impairment, elderly persons and hospitalized patients. The evidence indicates that these drugs are highly effective and safe in the elderly and in the presence of mild, moderate and severe renal failure improving glycemic control with low risk of hypoglycemia. In addition, several randomized-controlled trials have shown that the use of DPP4 inhibitors in combination with basal insulin represents an alternative to the basal-bolus insulin regimen in hospitalized patients with type 2 diabetes.

Keywords: Alogliptin; Basal insulin; DPP4 inhibitors; Glycemic control; Linagliptin; Saxagliptin; Sitagliptin; Type 2 diabetes; Vildagliptin

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INTRODUCTION

Type 2 diabetes mellitus (T2D) is a complex and progressive disease with an alarming increase worldwide. The International Diabetes Federation estimates that there are about 415 million adults aged 20–79 with diabetes, including 193 million who are underdiagnosed [1]. Distressingly, by the end of 2040, 642 million people will be living with the disease. T2D is characterized by multiple pathophysiologic defects, including progressive β-cell dysfunction and

insulin resistance in the liver and peripheral tissues [2]. Chronic hyperglycemia in diabetes is associated with increased risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (coronary artery, cerebrovascular or peripheral arterial disease) complications, leading to increased all-cause mortality [3]. Improved glycemic control to a target HbA1c concentration of 7.0% or lower is generally recommended to minimize the risk of long-term complications. However, about half of patients with diabetes remained with HbA1c $> 7\%$, and $\sim 15\%$ with HbA1c $> 9\%$, which placed them at high risk for complications and associated medical and indirect costs [4].

Current pharmacologic agents focus on the multiple pathophysiologic disturbances of T2D aiming at increasing available insulin, reducing resistance to insulin, slowing gastric emptying and absorption of carbohydrates, or promoting urinary glucose excretion. Dipeptidyl peptidase-4 (DPP4) inhibitors and GLP-1 receptor agonists (incretin agents) improve glucose control through several of these mechanisms, including a glucose-dependent reduction of postprandial glucagon or enhancement of insulin secretion as well as delayed gastric emptying [5–7]. DPP4 inhibitors are oral antidiabetic drugs that inhibit the enzyme DPP-4. DPP-4 is a ubiquitous enzyme expressed on the surface of most cell types that deactivates some bioactive peptides, including the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 [8, 9]. Clinical studies to date indicate that DPP4 inhibitors increase native GLP-1, which effectively stimulates insulin secretion, suppresses glucagon release and improves glucose control in patients with T2D. These agents are well tolerated and have a low incidence of adverse effects [10].

A recent comprehensive systematic review of available add-on options to basal insulin treatment reported that all antidiabetic agents alone or in combination with basal insulin are effective in improving glycemic control [11]. However, the weight neutrality and lower risk of hypoglycemia of DPP4 inhibitors make them attractive in the recommended approach to patient-centered care and shared decision-making [12, 13]. The present review summarizes recent data on the combination of DPP4 inhibitors with insulin-based regimens in the management of patients with T2D. Three clinical scenarios in which insulin therapy is indicated—chronic kidney disease, elderly persons and hospital care—illustrate the added value of DPP4 inhibitors and insulin combination.

METHODS

Two healthcare documentation specialists performed a comprehensive review of the literature. Randomized-controlled studies, observational studies and case series analyses published between 2001 and 2017 in which the main objective was to assess the efficacy and safety of DPP4 inhibitors, including alogliptin, sitagliptin, vildagliptin, saxagliptin and linagliptin, in combination with insulin in T2D were selected.

The search was conducted according to the PICO methodology [14], which included patients with type 2 diabetes mellitus (“P”), treatment with DPP4 inhibitors and insulin as the intervention (“I”), placebo as the comparator (“C”), and glycemic control, HbA1c and/or body weight as main outcomes (“O”). Studies in which these variables could not be identified were excluded. Using the electronic databases PubMed and MEDLINE (US National Library of Medicine, Bethesda, MD, USA), reports published in English and Spanish were considered. The MeSH terms ‘diabetes mellitus, type 2,’ ‘metformin,’ ‘insulin,’ ‘dipeptidyl peptidase IV inhibitors,’ ‘alogliptin,’ ‘sitagliptin,’ ‘vildagliptin,’ ‘saxagliptin,’ ‘linagliptin,’ ‘kidney failure chronic’ and ‘aged’ were used. Also, these descriptors combined with the free terms ‘add-on,’ ‘glucose-lowering,’ ‘elderly,’ ‘HbA1c,’ ‘weight’ and ‘incretin’ limited to the title or title/abstract fields were used. No other restrictions regarding article type or text availability were included in the search strategy. However, customized searches with the filter ‘Clinical Trial’ were also performed. The reference lists of the identified articles were manually searched for additional studies that may have been overlooked using the computer-assisted search strategy. Moreover, we searched http://www.

ClinicalTrials.gov for ongoing or completed clinical trials with DPP4 inhibitors added to basal insulin in T2D with inadequate glycemic control.

All articles were initially screened by reviewing the title and abstract; those articles in which the PICO approach could be applied were retrieved for full evaluation. Articles with the primary outcome aiming to assess the use of DPP4 inhibitors as add-on therapy to insulin were included in the analysis.

Selected studies were grouped according to each oral DPP4 inhibitor agent: alogliptin, sitagliptin, vildagliptin, saxagliptin and linagliptin. Studies focused on patients with T2D and renal impairment, the elderly population, and inpatient hospital and long-term care were independently evaluated. When a particular DPP4 inhibitor drug was primarily evaluated in patients with renal impairment or elderly subjects, results of these studies are presented in separate sections.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

COMBINATION THERAPY OF DPP4 INHIBITORS AND INSULIN: GENERAL OVERVIEW

Alogliptin

Results from randomized-controlled trials have shown that oral alogliptin improved glycemic control when administered as monotherapy, as dual therapy in combination with metformin, pioglitazone, a sulfonylurea, voglibose or insulin, or as triple therapy in combination with metformin plus pioglitazone [15]. Alogliptin was generally well tolerated and weight neutral, with a low risk of hypoglycemia.

Limited data are available on alogliptin treatment as add-on to insulin therapy (Table 1). In a randomized, double-blind, placebo-controlled study, alogliptin at daily doses of 25 mg or 12.5 mg was more effective than placebo to reduce HbA1c after 26 weeks of treatment, without causing weight gain or increasing the incidence of hypoglycemia [16]. Similar results were reported at 12 weeks in another trial of alogliptin plus insulin compared with placebo plus insulin conducted in Japanese patients [17]. In this trial, the incidence of AEs was comparable between groups, with no relevant increases in hypoglycemia or weight gain.

Sitagliptin

A 24-week randomized, double-blind, placebo-controlled study evaluated the efficacy and tolerability of sitagliptin when added to insulin therapy in T2D patients [18]. The addition of sitagliptin (100 mg/day) significantly reduced HbA1c by 0.6% compared with placebo (0.0%), with a higher proportion of patients achieving an HbA1c level $< 7\%$. In that study, a similar HbA1c reduction was observed with different insulin formulations (long-acting, intermediate-acting or premixed insulins). In a different 24-week randomized trial, the addition of sitagliptin to insulin was significantly more effective at lowering HbA1c levels compared with placebo, as well as a 25% lower insulin requirement, and showed a significant reduction in hypoglycemia and weight gain compared with an insulin titration regimen [19].

In a 24-week prospective, randomized, open-labeled, controlled trial carried out in Japan, patients who were suboptimally controlled with at least twice daily injection of insulin were assigned to continuation of insulin treatment or addition of sitagliptin to insulin treatment [20]. Adding sitagliptin to insulin significantly reduced HbA1c from $7.9\% \pm 1.0\%$ at baseline to $7.0\% \pm 0.8\%$ at week 24, while there was no significant change in HbA1c in the insulin group. The incidence of hypoglycemia was also significantly reduced in the sitagliptin added group [20]. In a randomized placebo-controlled trial in Chinese patients on a stable insulin regimen for ≥ 10 weeks, with or without metformin, and inadequate glycemic control, the addition of sitagliptin led to a significantly greater HbA1c reduction compared with placebo at week 24 [21]. A significantly higher proportion of patients taking sitagliptin (16%)

Table 1 Salient data of the main randomized studies of DPP4 inhibitors added to basal insulin therapy in patients with type 2 diabetes (T2D) and insufficient glycemic control

References	Design	Primary outcome	Patients and treatment	Main findings
Rosenstock et al. [16]	Randomized double-blind placebo-controlled	Change of HbA1c at week 26	Alogliptin 12.5 mg (n = 131) Alogliptin 25 mg (n = 129) Placebo (n = 130)	HbA1c change: − 0.71% for 25 mg dose, − 0.63% for 12.5 mg dose; − 0.13% placebo Decreases of HbA1c ≥ 0.5%, 1% and 1.5% significantly greater in alogliptin vs. placebo
Kaku et al. [17]	Randomized double-blind placebo-controlled	Change of HbA1c at week 12	Alogliptin 25 mg (n = 179)	HbA1c change: − 0.96% alogliptin vs. − 0.29% placebo; intergroup difference − 0.66%. Proportions of patients who achieved HbA1c < 8.0%, < 7.0% and < 6.0% were significantly higher in alogliptin group
Vilsbøll et al. [18]	Randomized placebo-controlled	Change of HbA1c at week 24	Sitagliptin 100 mg/day (n = 322) Placebo (n = 319)	HbA1c reduction 0.6% sitagliptin vs. 0% placebo HbA1c < 7% in 13% sitagliptin vs. 5% placebo Higher reductions of fasting glucose (15.0 mg/dl) and 2-h postmeal (36.1 mg/dl) relative to placebo
Hong et al. [19]	Randomized active-competitor parallel-group	Change of HbA1c at week 24	Sitagliptin 100 mg/day (n = 70) Insulin-increasing arm (n = 70)	HbA1c decreases − 0.6% vs. − 0.2%; hypoglycemic events 7.0 vs. 14.3 per patient-year; weight increase in the insulin-increasing subjects
Shankar et al. [21]	Randomized double-blind placebo-controlled	Change of HbA1c at week 24	Sitagliptin 100 mg/day (n = 234) Placebo (n = 233)	HbA1c reduction 0.7% vs. 0.3%; HbA1c target of < 7%: 16% vs. 8%; reduction of 2-h postmeal glucose 26.5 mg/dl relative to placebo; no change of body weight
Mathieu et al. [22]	Randomized double-blind placebo-controlled	Change of HbA1c at week 24	Sitagliptin 100 mg/day (n = 329) Placebo (n = 329)	HbA1c reduction − 1.3% vs. − 09%; increase in dose of insulin was less in the sitagliptin group (− 4.7 IU); fewer patients in the sitagliptin group experienced hypoglycemia
Yki-Järvinen et al. [24]	Randomized placebo-controlled	Change of HbA1c at week 24	Linagliptin 5 mg/day (n = 631) Placebo (n = 630)	HbA1c mean change − 0.58% vs. + 0.07% at 24 weeks, − 0.48% vs. + 0.05% at 52 weeks; HbA1c < 7.0% after 52 weeks: 16% vs. 7%; reduction in HbA1c ≥ 0.5%: 37% vs. 17%

Table 1 continued

References	Design	Primary outcome	Patients and treatment	Main findings
Sheu et al. [25]	Randomized placebo-controlled (post hoc analysis)	Change of HbA1c at week 24	Linagliptin 5 mg/day (n = 80) Placebo (n = 74)	HbA1c placebo-corrected mean change was − 0.9% ± 0.1% at weeks 24 and 52; changes in mean body weight − 0.67 vs. − 0.38 kg
Durán-Garcia et al. [26]	Randomized placebo-controlled (post hoc analysis)	Change of HbA1c at week 24	Linagliptin 5 mg/day (n = 475) Placebo (n = 475	HbA1c adjusted mean change − 0.63% vs. 0.04 at week 24; HbA1c ≤ 7%: 16.4% vs. 6.5% at week 52; placebo-corrected adjusted mean reduction of fasting plasma glucose -0.8 mmol/l at week 24; mean change of insulin dose 2.3 U vs. 4.0 U at week 52 versus baseline
Barnett et al. [27]	Randomized placebo-controlled	Change of HbA1c at week 24	Saxagliptin 5 mg/day (n = 304) Placebo (n = 151)	HbA1c change − 0.73% vs. − 0.32%; HbA1c < 7%: 17.3% vs. 6.7%; adjusted-mean change fasting plasma glucose − 10 vs. − 6 mg/dl
Barnett et al. [28]	Randomized placebo-controlled	Change of HbA1c at week 52	Saxagliptin 5 mg/day (n = 304) Placebo (n = 151)	Adjusted mean change HbA1c − 0.75% vs. − 0.38%; adjusted between-group difference − 0.37%; HbA1c < 7%: 21.3% vs. 8.7%; increase mean total insulin dose 5.67 vs. 6.67 U; similar results in metformin-treated patients
Li et al. [29]	Randomized-controlled open label	Changes of MAGE by CGM	Saxagliptin 5 mg/day (n = 31) Continuous subcutaneous insulin infusion (n = 38)	After 4 weeks of therapy, glycemic control reached in 3.62 vs. 4.54 days; total daily dose insulin 16.16 vs. 21.12 U; MAGE 2.47 vs. 3.37; hourly mean glucose levels (0:00–6:00 a.m.) lower in the saxagliptin group
Fonseca et al. [30]	Randomized placebo-controlled	Change of HbA1c at week 24	Vildagliptin 50 mg bid (n = 144) Placebo (n = 152)	HbA1c mean change − 0.5 vs. − 0.2% (between-group difference − 0.3%); increase in total daily insulin dose + 1.2 vs. + 4.1 U; hypoglycemia events 1.95 vs. 2.96 per patient-year (severe 0 vs. 0.10)
Kothny et al. [32]	Randomized placebo-controlled	Change of HbA1c at week 24	Vildagliptin 50 mg bid (n = 228) Placebo (n = 221)	HbA1c mean change − 0.8 vs. − 0.1% (between-group difference − 0.7%; − 0.6% in the presence of metformin, − 0.8% without metformin); similar hypoglycemic events (8.4% vs. 7.2%); no weight gain

Table 1 continued

References	Design	Primary outcome	Patients and treatment	Main findings
Hirose et al. [33]	Randomized placebo-controlled	Change of HbA1c at week 12	Vildagliptin 50 mg bid (n = 76) Placebo (n = 75)	HbA1c mean change − 1.01% vs. − 0.11% (between-group difference − 0.91%); HbA1c < 7%: 50% vs. 3.9%; reductions in FPG higher in the vildagliptin group
Ning et al. [34]	Randomized placebo-controlled	Change of HbA1c at week 24	Vildagliptin 50 mg bid (n = 146) Placebo (n = 147)	Adjusted mean change HbA1c − 1.08% vs. − 0.38% (between-group difference − 0.7%); HbA1c < 7%: 23.6% vs. 11.2%; hypoglycemia 2.7% vs. 5.4%

MAGE mean amplitude glycemic excursion, *CGM* continuous glucose monitoring, *bid* twice a day, *FPG* fasting plasma glucose

had an HbA1c of < 7.0% compared with placebo (8%) at week 24. Also, the addition of sitagliptin significantly reduced 2-h postmeal glucose by 26.5 mg/dl relative to placebo. Neither group had a significant change from baseline in body weight [21]. The addition of sitagliptin prior to intensive titration of basal insulin glargine has been shown to reduce the insulin requirements while providing superior glycemic control and less hypoglycemia compared with an insulin-titration regimen [22] (Table 1).

In a study using continuous glucose monitoring (CGM), the addition of sitagliptin led to significant decreases in 24-h mean glucose levels and reduction in glycemic variability compared with insulin therapy alone [23].

Linagliptin

The long-term effect of linagliptin as add-on therapy to basal insulin alone or in combination with metformin and/or pioglitazone was evaluated in a 52-week phase 3 randomized, placebo-controlled study [24] (Table 1). The adjusted mean changes in HbA1c from baseline were significantly higher in the linagliptin than placebo group, with treatment differences maintained for 76 weeks. Also, the proportion of patients with a reduction in HbA1c ≥ 0.5% was higher in the linagliptin group without an increase in hypoglycemia or body weight. Similar results were obtained in a post hoc analysis in the subset of Asian patients [25] as well as in a subanalysis of participants on basal insulin and also on metformin [26].

Saxagliptin

The efficacy and safety of saxagliptin as add-on therapy were evaluated in a randomized placebo-controlled study in which 455 patients with T2D with inadequate glycemic control were on insulin alone [27] (Table 1). Patients were assigned 2:1 to receive saxagliptin (5 mg/day) or placebo for 24 weeks. Patients treated with saxagliptin had significantly greater reductions of HbA1c and postprandial glucose at 24 weeks than placebo. The difference in the proportion of patients achieving an HbA1c value < 7% was 17.3% and 6.7% of patients in the saxagliptin and placebo groups, respectively. HbA1c reduction in this study was not different between patients using metformin or not. Changes in body weight and confirmed hypoglycemia were similar in both groups. The favorable results associated with the combined use of saxagliptin and basal insulin were confirmed in a 28-week extension analysis of the same trial [28]. A randomized-controlled open-label study using CGM in patients with T2D treated with continuous subcutaneous insulin infusion also showed saxagliptin improved

glycemic control with lower insulin dose requirements [29].

Vildagliptin

Fonseca et al. [30] published the first study with vildagliptin in combination with insulin in 2007. In this 24-week randomized, double-blind, placebo-controlled trial, HbA1c levels decreased by − 0.3% compared with placebo, without differences in body weight. Lower number and severity of hypoglycemic episodes were reported with vildagliptin compared with placebo. In a double-blind 28-week extension (overall treatment period 1 year), the hypoglycemic benefit was still evident and the improvement in glycemic control was sustained in patients continuing on vildagliptin 50 mg twice a day [31]. A different 24-week randomized, double-blind study compared the effects of vildagliptin (50 mg twice a day) and placebo as add-on to ongoing insulin therapy, with or without metformin [32]. Vildagliptin reduced HbA1c by 0.8%, with a between-group difference of − 0.7% compared with placebo. Treatment was not associated with weight gain or with increased risk of hypoglycemia. In two additional randomized-controlled studies in Japanese [33] and Asian, predominantly Chinese, patients with T2D and inadequate diabetes control, the addition of vildagliptin to basal insulin, with or without concomitant metformin, significantly improved glycemic control without an increased risk of hypoglycemia [33, 34].

Real-World Studies on the Combination of DPP4 Inhibitors and Insulin

Two real-world studies have reported improvements in glycemic control in patients with T2D inadequately controlled on insulin treated with the addition of DPP4 inhibitors without causing significant weight gain or increasing the incidence of hypoglycemia [35, 36]. The role of DPP4 inhibitors added to basal insulin has also been tested on a real-world basis in a particular clinical situation after switching from premixed insulin to basal insulin [37]. Administering DPP4 inhibitors within this regimen may contribute to improving patients' glycemia, with a favorable weight-change profile and without increasing hypoglycemia risk.

DPP4 INHIBITORS IN CHRONIC RENAL DISEASE

Diabetic nephropathy is now the most common cause of chronic kidney disease (CKD) [38]. A cross-sectional analysis of adults with T2D based on the US National Health and Nutrition Examination Survey (NHANES) during 2007–2012 showed a CKD prevalence of 38.3% [39]. Kidney involvement both directly and indirectly increases the damage of other organs and increases morbidity and mortality in patients with diabetes.

Although it has been widely recognized that prevention and early diagnosis of diabetic nephropathy improve long-term outcomes, management of hyperglycemia in patients with CKD is especially challenging, mainly because of changes in the renal excretion of antidiabetic drugs and comorbidities frequently present in these patients. Hypoglycemia and depletion of volume-associated adverse events risks are increased. The choice of antidiabetic agents for the management of patients with T2D and CKD is limited. Some pharmacologic classes are contraindicated in moderate or severe CKD, such as metformin, sulfonylureas and SGLT2 inhibitors. Insulin has been considered the safe choice for treating patients with kidney injury [40]. However, it requires a delicate dose adjustment because of changes in its duration of action and the augmented hypoglycemic risk in CKD [41].

Available evidence indicates that the use of DPP4 inhibitors effectively lowers HbA1c and may be safe in patients at various stages of renal insufficiency [42–51]. All DPP4 inhibitors are appropriate pharmacotherapeutic choices in patients with declining renal function, with linagliptin affording the added advantage of not requiring dose adjustment because it is not excreted through the kidney [48]. Recommendations for the use of DPP4 inhibitors in the

presence of renal impairment are shown in Table 2.

Few studies have assessed the efficacy of DPP4 inhibitors as add-on therapy in patients with T2D and CKD. In an analysis of 811 participants in two phase-3 randomized placebo-controlled trials of linagliptin, placebo-adjusted mean HbA1c changes from baseline were − 0.59% (mild renal impairment) and − 0.69% (moderate renal impairment) after 24 weeks and − 0.43% (severe renal impairment) after 12 weeks [49] of therapy. Frequency of hypoglycemia in patients treated with linagliptin with mild, moderate and severe renal impairment was 34.9%, 35.6% and 66.7%, respectively, compared with 37.5%, 39.7% and 49.1% in patients treated with placebo. Episodes of severe hypoglycemia were low (< 5.6%) in both treatment arms [49]. A subanalysis of a 24-week randomized placebo-controlled study of vildagliptin 50 mg/day in 178 patients with T2D and renal disease, including patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) while receiving ongoing insulin therapy reported that vildagliptin is a suitable treatment option in these patients [50]. The adjusted mean change in HbA1c from baseline (7.7% ± 0.1%) was − 0.9% ± 0.4% and the between-treatment difference was −0.6% ± 0.2%. The percentage of patients achieving endpoint HbA1c < 7.0% was 45.2% with vildagliptin and 22.8% with placebo. Vildagliptin and placebo had comparable hypoglycemic profiles and did not cause weight gain.

In summary, DPP4 inhibitors are a useful treatment option in people with T2D and CKD. DPP4 inhibitors, alone or in combination with insulin, are an effective and safe option across a wide range of renal functions [51].

Table 2 Use of DPP4 inhibitors in patients with type 2 diabetes and renal function impairment

Drug	Comment
Alogliptin	Doses should be halved in moderate-to severe renal failure
	eGFR 30–50 mL/min/1.73 m^2: halve doses
	eGFR < 30 mL/min/1.73 m^2: quarter doses
Linagliptin	Dose adjustment is not needed
Sitagliptin	Doses should be halved in moderate-to severe renal failure
	Should be avoided in end-stage renal disease or hemodialysis
Sitagliptin	Doses should be halved in moderate-to severe renal failure
	eGFR 30–50 mL/min/1.73 m^2: halve doses
	eGFR < 30 mL/min/1.73 m^2: quarter doses
Vildagliptin	Doses should be halved in moderate-to severe renal failure
	Use with caution in end-stage renal disease or hemodialysis

eGFR estimated glomerular filtration rate

DPP4 INHIBITOR USE IN ELDERLY PATIENTS

Treatment of T2D in the elderly is a major challenge because of the heterogeneity of this population with different functional and cognitive capacities, the presence of comorbidities and greater risk of hypoglycemia [52]. To minimize the risk of hypoglycemia and maximize the benefits of glycemic control, guidelines typically recommend individualizing HbA1c targets based on life expectancy, functional status and individual goals [53]. Safety is more important than reduction of HbA1c in the elderly. Although many elderly patients with T2D require insulin therapy to achieve and maintain glycemic control, treatment should be tailored to meet the needs of each individual [54]. The need to set individualized HbA1c targets using agents associated with a low risk of hypoglycemia has been suggested [55]. Metformin is the drug of choice, but its use is limited by the presence of gastrointestinal side effects, weight loss and reduced kidney function in the elderly population [53]. The use of DPP4 inhibitors has been shown effective in the elderly and frail population [55].

The results of a 6-month open randomized-controlled trial (Linagliptin-LTC Trial) in 140 elderly residents with T2D in long-term care

facilities treated with linagliptin (5 mg/day) or with low-dose basal insulin (starting dose 0.1 U/kg/day), with or without metformin, were recently reported [56]. The primary outcome was the mean difference in daily fasting or premeal blood glucose. Treatment with linagliptin resulted in similar glycemic control but a significantly lower risk of hypoglycemia (< 70 mg/dl, 3% vs. 37%) compared with basal insulin therapy.

A pooled analysis of ten studies of 24-week duration with vildagliptin (50 mg twice daily) in 301 patients ≥ 75 years showed that this agent was effective and well tolerated [57]. Results of a 24-week randomized placebo-controlled study of linagliptin (5 mg/day) administered because of insufficient glycemic control despite metformin and/or sulfonylurea and/or insulin therapy in 241 patients aged ≥ 70 years showed the adjusted mean change from baseline in HbA1c between linagliptin and the placebo was − 0.64% and − 1.15 mmol/l in fasting blood glucose [58]. The target treatment outcome of HbA1c < 7.0% was achieved significantly more often in patients on linagliptin treatment than in those with placebo (38.9% vs. 8.3%). Hypoglycemia was the most common adverse event in both groups, but did not differ between groups. Similar favorable results were obtained in a 24-week randomized placebo-controlled study of combined treatment of vildagliptin and insulin [30]. In a pre-planned subgroup analysis of elderly patients aged 65 years or more, the adjusted mean change of HbA1c was − 0.7% ± 0.1% during treatment with vildagliptin and − 0.1% ± 0.1% during placebo administration (between-group difference − 0.6%). Confirmed hypoglycemia was somewhat lower in the vildagliptin group (2.32 vs. 2.64 events per patient-year). Elderly subjects can have greater postprandial glucagon and glucose levels than younger people; therefore, suppression of inappropriate glucagon secretion mediated by vildagliptin may explain the higher efficacy observed in an elderly population with T2D [30]. In summary, it seems that combined treatment of DPP4 inhibitors and insulin is effective in achieving glycemic control in elderly patients with T2D.

DPP4 INHIBITORS IN HOSPITALIZED PATIENTS

Randomized clinical trials carried out in critically and non-critically ill medical and surgical patients have shown that improvement of glycemic control reduced the risk of comorbidities such as systemic infections, length of hospital stay [66–68] and mortality [59–61]. Insulin therapy is required for glycemic control in a considerable proportion of patients in the hospital [62]. Some of them are treated with intravenous infusion during acute and severe intercurrent illness (as in the ICU). Subcutaneous insulin administration is used more frequently in non-critical wards. Clinical guidelines recommend basal-bolus insulin regimens as the standard of care for these patients with T2D [63, 64]. However, basal-bolus insulin regimens require multiple daily insulin injections and carry a substantial risk of hypoglycemia, reported in up to 32% of non-ICU patients with T2D [65]. Thus, simple regimens that result in similar glycemic efficacy to basal-bolus insulin with less frequency of hypoglycemia are needed to improve care for non-critically ill patients with diabetes.

Recent randomized-controlled studies of non-critically ill medical and surgical patients have reported that treatment with a DPP4 inhibitor alone or in combination with insulin glargine results in similar glycemic control with less hypoglycemia than glargine and rapid-acting insulin with meals [66–68]. Our group first reported a pilot study in non-critical patients with blood glucose levels between 140 and 400 mg/dl treated with diet, oral antidiabetic drugs or low-dose insulin (≤ 0.4 U/kg/day) who were randomized to sitagliptin once daily, sitagliptin and basal insulin, or basal-bolus insulin [66]. Doses of rapid insulin before meals and bedtime were used for correcting blood glucose > 140 mg/dl. Sitagliptin alone or in combination with basal insulin resulted in similar mean daily blood glucose, hypoglycemia risk and treatment failures compared with the basal-bolus regimen. This study was followed by the SITA-HOSPITAL trial, a multicenter, randomized-controlled trial comparing sitagliptin and

basal insulin to the more complex basal-bolus insulin regimen in patients with T2D [67]. A total of 279 patients previously treated with oral antidiabetic agents or low-dose insulin (< 0.6 U/kg/day) and between 18 and 80 years of age were included. This strategy resulted in non-significant differences in the glycemic control, hypoglycemic rate, hospital length of stay, treatment failures and hospital complications compared with a standard basal-bolus regimen [67]. Additionally, it was associated with a significant reduction in both the total daily insulin dose and insulin injections [67]. Recently, Garg et al. [68] reported that treatment with saxagliptin in subjects with T2D and mild-to-moderate hyperglycemia was also associated with similar glucose control compared with basal or basal-bolus insulin therapy. This evidence indicates that the use of DPP4 inhibitors alone or in combination with basal insulin represents a new step in the future of inpatient hyperglycemia management [69]. Salient findings of these studies are shown in Table 3.

SUMMARY

Treatment intensification is a consistent need for patients with T2D. As β-cell function declines with disease progression, combination oral antidiabetic therapy is needed to attain glycemic control. Insulin therapy has historically been the next line of treatment alone or in combination with oral agents. Many studies have reported that weight gain and hypoglycemia may limit the ability to titrate insulin to achieve optimal glycemic control.

DPP4 inhibitor plus insulin is an effective and safe approach to optimize the management of glycemic control without increasing the risk of hypoglycemia or excessive weight gain. Most patients treated with this combination consistently showed a reduction in insulin requirement, better glycemic control, reduction in glycemic variability and a lower risk of hypoglycemia. The efficacy and safety of this combination have been proven with different DPP4 inhibitors, including alogliptin, sitagliptin,

Table 3 Salient data of studies of DPP4 inhibitors in hospitalized patients with T2D

References	Design	Patients and treatment	Main findings
Umpierrez (2013) [66]	Pilot randomized study	90 in-patients; sitagliptin alone or combined with glargine or a basal-bolus (glargine and lispro) both with correctional insulin doses	No differences in glycemic control, length of hospital stay and hypoglycemia events Fewer total daily insulin doses and numbers of insulin injections in sitagliptin groups
Pasquel (2017) [67]	Non-inferiority randomized-controlled trial	277 in-patients; sitagliptin plus basal glargine once daily or basal-bolus (glargine and lispro) both with correctional insulin doses	Mean daily glucose concentration was non-inferior No differences in hospital complications, length of stay, hypoglycemic events and treatment failures
Garg (2017) [68]	Randomized-controlled trial	66 in-patients; saxagliptin or basal-bolus insulin therapy, both with correctional insulin doses	Non-inferior in mean daily blood glucose control Lower glycemic variability Basal-bolus insulin: higher number of injections and daily insulin dose

linagliptin, saxagliptin and vildagliptin in randomized, double-blind, placebo-controlled clinical studies. Rare but severe adverse events associated with DPP4 inhibitors such as pancreatitis, heart failure (saxagliptin) and bullous pemphigoid have been reported [8].

DPP4 inhibitors added to basal insulin improve glycemic control without increasing the risk of hypoglycemia. However, not all the studies showed consistent results. This may be due to the different protocols used.

It should be noted that insulin doses may be reduced when the DPP4 inhibitor + insulin combination is performed and that it also is recommended to reduce the dose of SU when DPP4 inhibitors are added to this treatment.

A subgroup of patients with a high risk of hypoglycemia, such as those with renal impairment and elderly patients, represents prime candidates to receive treatment with DPP4 inhibitors with or without low-dose insulin therapy. In addition, increasing evidence indicates that incretin-based therapies have the potential to improve glycemic control with a low risk of hypoglycemia in hospitalized patients with mild-to-moderate hyperglycemia [66–68].

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