The efficacy and safety of dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus patients with severe renal impairment: a meta-analysis

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ABSTRACT

Aims/introduction Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral antidiabetic agents, and have been increasingly and widely used in the treatment of diabetes mellitus (DM). However, information of DPP-4 inhibitors in type 2 DM patients with severe renal impairment (RI) is limited. Our study aimed to assess the efficacy and safety of DPP-4 inhibitors as compared to placebos or other hypoglycemic drugs in type 2 DM patients with severe RI.

Materials and methods A meta-analysis was conducted to examine the literature comparing the effects of DPP-4 inhibitors on hemoglobin A1c (HbA1c) and fasting blood glucose (FBG). Randomized control trials (RCTs) including adults with type 2 DM and severe RI were analyzed. Safety was evaluated based on the percentage of patients who developed hypoglycemia and the occurrence of adverse events (AEs) as well as the incidence of peripheral edema, urinary tract infection, diarrhea, and death.

Results Five RCTs including 503 patients were analyzed. Compared with a placebo or no treatment, DPP-4 inhibitors were associated with a larger decline in HbA1c (mean difference (MD) = −0.57, 95% confidence interval (CI): −0.73 to −0.41; p < 0.01) but not with FBG (MD = −0.26, 95% CI: −1.40 to 0.8; p = 0.66). Compared with glipizide monotherapy, no significant differences in HbA1c (MD = 0.15, 95% CI: −0.19 to 0.49; p = 0.38) or FBG (MD = −0.26, 95% CI: −1.16 to 0.64; p = 0.57) were found. Similar odds of experiencing an AE were found in both the DPP-4 inhibitor groups and comparison groups.

Conclusions In type 2 DM patients with severe RI, treatment with DPP-4 inhibitors is safe and it effectively lowers HbA1c.

Introduction

Diabetes is a leading cause of end-stage renal disease, and hyperglycemia in patients with renal impairment (RI) is difficult to manage because of the limited therapeutic options and high prevalence of comorbidities. Longstanding type 2 diabetes in patients with advanced kidney disease often requires insulin therapy; however, finding the appropriate insulin dosage is a significant challenge in a renally impaired population because of impaired catabolism and insulin clearance. Metformin, the most commonly used antihyperglycemic agent for type 2 diabetes mellitus (DM), is contraindicated in diabetic patients with RI because it is excreted renally. For the same reason, the usefulness of sulfonylureas and thiazolidinediones is limited in patients with RI. Thus, treatment options available for these patients are restricted because of safety and tolerability issues.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including sitagliptin, vildagliptin, saxagliptin, and linagliptin, are a relatively new class of oral hypoglycemic drugs. DPP-4 inhibitors may be beneficial for preventing diabetic complications and modulating glucagon like peptide-1 receptor expression as they are well tolerated in individuals with type 2 DM and have a low incidence of hypoglycemia when used alone or with antihyperglycemic agents.

Previous systematic reviews of randomized controlled trials have assessed the efficacy and safety of DPP-4 inhibitors in the general diabetes population, however, studies regarding populations with type 2 DM with renal insufficiency are limited. Therefore, we aimed to conduct a meta-analysis to assess the efficacy and safety of DPP-4 inhibitors for the treatment of type 2 DM in patients with severe RI.
Materials and methods

Search strategy

We conducted an extensive literature search using the PUBMED, EMBASE, and Cochrane Central Register of Controlled Trials databases for articles published before August 2014. We used key terms such as “DPP-4,” “dpp-iv,” “dipeptidyl peptidase iv,” “renal failure,” “renal insufficient,” and “renal impairment” in combination with relevant MeSH terms for this search. We did not restrict the publication year or publication language of the studies. Reference lists of the identified relevant studies were also reviewed for any additional articles that may have been missed.

Selection criteria

Studies were included if they 1) used a randomized controlled trial design; 2) were conducted over at least 24 weeks; 3) included type 2 DM patients with severe RI (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²), including dialysis patients; and 4) compared DPP-4 inhibitors with a placebo or other glucose-lowering medications. Any disagreements between the reviewers were discussed until a consensus was reached.

Data analysis

Two independent investigators assessed the titles and abstracts of all potentially relevant citations and reviewed the full-text of articles that met the inclusion criteria. Information concerning the characteristics of the studies (e.g., study design, sample size, follow-up duration, and publication year), baseline characteristics of participants (e.g., age, sex, renal function, intervention regimen, and hemoglobin A1c (HbA1c) levels), and outcomes regarding efficacy and safety was extracted from each relevant study. Changes in HbA1c and fasting blood glucose (FBG) levels between the baseline and final follow-up examinations were evaluated to measure efficacy. The percentage of patients with hypoglycemia and the occurrence of any adverse event (AE) or any serious AE (SAE) as well as the incidence of peripheral edema, urinary tract infection, diarrhea, and death were evaluated to measure safety.

Risk of bias assessment

The risk of bias was assessed using the guidelines published by the Cochrane Collaboration. The Cochrane Collaboration’s tool for evaluating the risk of bias examines seven domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain is then assigned a bias summary: low risk of bias, high risk of bias, or unclear risk of bias.

Statistical analyses

We calculated the odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous variables. Statistical heterogeneity across studies was analyzed using Cochran’s Q test (heterogeneity χ²) and the I² statistic. A fixed-effects model was used when the I² value was <50%, and a random-effects model was used when the I² value was >50%. A p-value <0.05 was considered statistically significant. All statistical analyses were conducted with Review Manager 5, version 5.3 (The Cochrane Collaboration, 2014, http://ims.cochrane.org/revman).

Results

Literature search and study characteristics

Five studies extracted from 1829 potentially relevant articles met the eligibility criteria. The detailed steps of the study selection process are summarized in Figure 1 and the characteristics of the included studies are described in Table 1. All trials were randomized controlled trials (RCTs) and included a total of 503 patients. One of the five trials included patients with an eGFR <50 mL/min, but we extracted data only for patients with severe RI (eGFR <30 mL/min). Four trials compared a DPP-4 inhibitor with a placebo and one directly compared a DPP-4 inhibitor with glipizide.

Methodological quality was assessed through a domain-based evaluation tool recommended by the Cochrane Collaboration. The risk of bias for the included studies is summarized in Figure 2. Funnel plot asymmetry was not assessed because only five RCTs were included in our meta-analysis.

Efficacy

HbA1c. All five trials investigated the difference in HbA1c before and after treatment. Four trials compared DPP-4 inhibitors against a placebo or no treatment. The combined data showed that the MD for HbA1c post-treatment was statistically significant (MD = −0.57, 95% CI: −0.73 to −0.41; p < 0.01; I² = 0%; Figure 3); however, the trial comparing DPP-4 inhibitors with glipizide found that the change in HbA1c was not significant between groups (MD = 0.15, 95% CI: −0.19 to 0.49; p = 0.38;
I2 = 0%; Figure 3). The pooled data from all five trials showed that improvements in HbA1c remained significant (MD = −0.43, 95% CI: −0.58 to −0.29; p < 0.01; Figure 3), but a substantial amount of heterogeneity (I2 = 82%) was found.

FBG. Four trials investigated the difference in FBG before and after treatment. Three trials compared DPP-4 inhibitors with a placebo or no treatment, and the pooled data showed no statistically significant difference between the groups (MD = −0.26, 95% CI: −1.40 to 0.8; p = 0.66; I2 = 71%; Figure 4). The results of the trial comparing DPP-4 inhibitors and glipizide showed that both DPP-4 inhibitors and glipizide similarly reduced FBG (MD = −0.26, 95% CI: −1.16 to 0.64; p = 0.57; Figure 4). Furthermore, the pooled data from all four studies regarding the change in FBG showed no statistically significant difference between groups (MD = −0.31, 95% CI: −1.08 to 0.47; p = 0.44; I2 = 58%; Figure 4).

Safety

Hypoglycemia. All five trials examined the incidence of hypoglycemia. Compared with placebos, we did not find that DPP-4 inhibitors significantly increased the risk of hypoglycemia (OR = 1.43, 95% CI: 0.89–2.3; p = 0.14; I2 = 0%; Figure 5). Similarly, no difference in the risk of hypoglycemia was found when comparing the DPP-4 inhibitor group and the glipizide group (OR = 0.55, 95% CI: 0.15–1.99; p = 0.36; Figure 5). Furthermore, when data
from all five trials were pooled, no significant difference regarding the incidence of hypoglycemia was found (OR = 1.27, 95% CI: 0.82–1.92; \( p = 0.29; I^2 = 0\%\); Figure 5).

Other AEs. All AEs observed in the studies are summarized in Table 2. In general, there was a similar incidence of mortality, AEs (including any AE, SAE, and drug-related AEs), and discontinuation due to an AE when comparing DPP-4 inhibitor groups with control groups. Three trials\(^4\,\,\,6\,\,\,7\) reported results regarding the change in renal status after treatment among patients. However, because of a lack of accurate eGFR values, we could not calculate the effect of DPP-4 inhibitors on renal function. Nonetheless, all of these trials reported that there was no clinical decrease in the eGFR in either the DPP-4 inhibitor group or the comparison group. Furthermore, DPP-4 inhibitors were not associated with a significantly higher risk of peripheral edema (OR = 0.66, 95% CI: 0.36–1.22; \( p = 0.74; I^2 = 0\%\)), urinary tract infection (OR = 0.95, 95% CI: 0.48–1.88; \( p = 0.13; I^2 = 51\%\)), or diarrhea (OR = 1.15, 95% CI: 0.59–2.24; \( p = 0.34; I^2 = 7\%\)).

**Discussion**

In the present meta-analysis, we conducted a comprehensive search for all studies examining DPP-4 inhibitors (including vildagliptin, sitagliptin, saxagliptin, and linagliptin) currently available for type 2 diabetes patients. However, only five RCTs included patients with type 2 diabetes and severe renal insufficiency. Nonetheless, our data showed that the decrease in HbA1c in the DPP-4 inhibitor groups versus the placebo or no treatment groups was significant in this population, results that are consistent with those found in previous meta-analyses.
regarding diabetes patients with normal renal function.\textsuperscript{2} However, DPP-4 inhibitors may be not superior to other hypoglycemic drugs (such as glipizide). In addition, as an add-on therapy, DPP-4 inhibitors did not show any effect when compared with a placebo, supporting the results of previous studies.\textsuperscript{3}

Hypoglycemia also exerts a large influence on mortality, morbidity, and the quality of life of diabetes patients.\textsuperscript{9} Therefore, prevention of hypoglycemia as part of the treatment strategy for type 2 diabetes patients is critical. Because the glucose-lowering effect of DPP-4 inhibitors is glucose dependent,\textsuperscript{10} the incidence of hypoglycemia is rare among patients receiving DPP-4 inhibitor monotherapy. However, hypoglycemia can still occur because DPP-4 inhibitors are often a second-line treatment administered in addition to metformin or insulin. Fortunately, our meta-analysis showed that DPP-4 inhibitors do not increase the risk of hypoglycemia when compared with a placebo or glipizide.

One previous study\textsuperscript{11} did report renal failure after treatment with DPP-4 inhibitors. However, the long-term safety of DPP-4 inhibitors and their effects on renal toxicity have not been clearly established by large RCTs. Although the pooled data in our meta-analysis was not sufficient to estimate the effect of DPP-4 inhibitors on renal safety, the included studies showed that the renal status of patients was stable at the final follow-up. Similarly, the SAVOR-TIMI 53 trail,\textsuperscript{12} which uses a pre-specified renal safety composite endpoint, showed that saxagliptin did not increase the risk of impaired kidney function. However, in spite of this, dose adjustment is recommended for all medications except linagliptin\textsuperscript{13} (because 80% of linagliptin is eliminated unchanged in feces\textsuperscript{14}).

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**Figure 4.** Forest plot shows the effect of DDP-4 inhibitors or comparators on FBG change when follow-up is finished.

**Figure 5.** Forest plot shows OR of the incidence of hypoglycemia between DDP-4 inhibitors and comparators.
In general, DPP-4 inhibitors are fairly tolerable and safe. Our meta-analysis did not find an increased risk of AEs, SAEs, or drug-related AEs in patients with severe RI. In addition, the rate of some relatively frequent DPP-4 inhibitor-related AEs (such as peripheral edema, urinary tract infection, and diarrhea) was not significantly larger than the rate associated with other treatments.

To our knowledge, this is the first meta-analysis examining DPP-4 inhibitor treatment in type 2 diabetes patients with severe RI. We conducted this analysis according to the Cochrane Handbook for Systematic Reviews of Interventions and tried to conduct a comprehensive search of the literature. Although all of the included studies were RCTs, several limitations of this meta-analysis should be acknowledged. First, only five studies were obtained, and no unpublished studies were included. As such, the data was not robust enough to compare the safety of DPP-4 inhibitors with other active therapies, such as glipizide. The limited number of studies and the relatively small sample size certainly influenced the power of our study. Second, few studies have examined the differences between individual DPP-4 inhibitors. As such, we did not assess each type of DPP-4 inhibitor separately; therefore, we were not able to perform a detailed meta-analysis. Third, sensitivity analyses to determine the effect of patient baseline characteristics (e.g., the disease course or baseline HbA1c levels) were not conducted. However, data from a previous meta-analysis suggested that these parameters had little effect on the change in HbA1c.

Finally, although the follow-up duration of studies in our meta-analysis was longer than 24 weeks, the duration was still too short to evaluate whether DPP-4 inhibitors increased the risk of some relatively uncommon AEs in chronic kidney disease patients. However, this is important because RI itself is a risk factor for some uncommon AEs, such as pancreatitis.

DPP-4 inhibitors are a useful second-line therapy for diabetes. DPP-4 inhibitors have been increasingly accepted as a treatment for type 2 diabetes patients with renal insufficiency. Our meta-analysis further demonstrates that DPP-4 inhibitors are effective and well tolerated by patients with severe RI. However, diabetes patients with kidney disease are heterogeneous. For example, patients with diabetes receiving peritoneal dialysis are exposed to a certain amount of glucose through dialysis, thus it is unclear whether DPP-4 inhibitors have a similar efficacy in this population. In conclusion, DPP-4 inhibitors are a safe and effective choice to help type 2 diabetes patients with severe RI achieve their glycemic targets.

Disclosure statement
The authors have declared that no competing interests exist.

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Ethical approval
This article does not contain any studies with human participants performed by any of the authors.

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