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Efficacy and safety of dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes mellitus patients with moderate to severe renal impairment: a meta-analysis

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Abstract. – OBJECTIVE: Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral antidiabetic agents for type 2 diabetes mellitus (T2DM) patients. However, the effects and safety of DPP-4 inhibitors in T2DM patients with renal impairment (RI) remain controversial. Therefore, we conducted this meta-analysis to assess the efficacy and safety of DPP-4 inhibitors in T2DM patients with moderate to severe RI.

MATERIALS AND METHODS: The PubMed, Embase, and Web of Science database were searched for published randomized controlled trials (RCTs), which compared DPP-4 inhibitors with placebo or a control regimen. A fixed-model effect or random-effect model was used to assess the effects of DPP-4 inhibitors on T2DM patients with RI. Subgroup analysis or meta-regression analysis were performed to explore the potential sources of heterogeneity among the included studies.

RESULTS: 13 RCTs with a total of 2,940 patients were included in this meta-analysis. Compared with other treatments, DPP-4 inhibitors were associated with a greater change in HbA1c level (weight mean difference (WMD)=-0.50, 95%CI: -0.61, -0.39; $p<0.001$), and a higher response rate of patients achieving the HbA1c goal of <7% (risk ratio (RR)=1.38, 95%CI: 1.12, 1.70; $p=0.002$). Subgroup analysis suggested that the reduced HbA1c was observed in all types of DPP-4 inhibitors, and in patients with moderate or severe RI, but not in those with end-stage renal disease. DPP-4 inhibitors did not significantly lower the FPG level (WMD=-0.36, 95%CI: -0.92, 0.20; $p=0.204$), and this was seen in all types of DPP-4 inhibitors except gemigliptin, which showed a significant reduction in FPG level. The prevalence of adverse events (RR=0.98, 95%CI: 0.94, 1.02; $p=0.256$) in the two groups was not significantly different, and DPP-4 inhibitors did not induce a higher rate of hypoglycemia (RR=1.31, 95%CI: 0.97, 1.77; $p=0.075$).

CONCLUSIONS: DPP-4 inhibitors significantly lowered HbA1c levels in T2DM patients with moderate to severe RI. And the treatment of DPP-4 inhibitors did not increase the risk of hypoglycemia and adverse events. Considering the potential limitations in this meta-analysis, more large-scale, well-conducted RCTs are needed to identify our findings.

Key Words
Type 2 diabetes mellitus, Dipeptidyl peptidase-4 inhibitor, Renal impairment, Meta-analysis.

Introduction

Type 2 diabetes mellitus (T2DM) is the leading cause of chronic kidney disease (CKD)[1]. Moderate to severe renal impairment (RI), which defined as an estimated glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2, occurred in 20-30% of patients[2,3]. Patients at this advantage of RI is difficult to manage because of the high prevalence of co-morbidities, increased risk of hypoglycemia[4], and reduced drug elimination rate[5]. Insulin therapy combined with oral antihyperglycemic drugs (OADs) is frequently used in patients with T2DM when their glycemic control deteriorates[3]. However, commonly used OADs are either contraindicated or should be used at reduced doses in individuals with RI[3]. Importantly, patients with T2DM and RI have an increased risk of hypoglycemia, which is commonly due to decreased clearance of insulinotropic agents[6]. Moreover, most OADs are affected by kidney

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function and should, therefore, be either or used at reduced doses in patients with CKD[5,7]. Consequently, additional treatment options suitable for patients with T2DM and CKD and which have a low risk of hypoglycemia are needed.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are relatively new oral hypoglycemic drugs. They could modulate fasting plasma glucose, postprandial glucose, and HbA1c levels by decreasing the inactivation of incretins such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide to stimulate the release of insulin in a glucose-dependent manner[8,9]. These agents include sitagliptin, vildagliptin, saxagliptin, and linagliptin. For patients with T2DM and CKD, these agents are suitable since they show good tolerability, low risk of hypoglycemia, and neutral effect on body effect.

Two systematic reviews and meta-analysis[10,11] regarding the DPP-4 inhibitors on reducing HbA1c level have been published. Both of them showed that DPP-4 inhibitors were effective at lowering HbA1c in T2DM patients with moderate or severe RI. However, one was only based on five randomized controlled trials (RCTs) and included relatively small sample size[10], and another included half of the studies published in the form of conferences abstracts, clinical trials registries, company websites, and FDA and EMA websites, without access to the full-data[11]. Moreover, the roles of different type of DPP-4 inhibitors on various CKD stages have not been well established. Recently, several relevant RCTs regarding DPP-4 inhibitors on reducing the HbA1c level have been published. These reports were well-performed RCTs and included an additional more than 1,356 patients. We, therefore, conducted this updated meta-analysis of 13 RCTs to evaluate the efficacy and safety of DPP-4 inhibitors for T2DM patients with moderate or severe RI.

Materials and Methods

Search Strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) criteria[12]. Two independent investigators searched the literature collected in PubMed, Embase, and Web of Science up to April 12, 2017. Electronical search was performed using the following search algorithm: ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND (DPP-4[All Fields] OR dppiv[All Fields] OR ("dipeptidyl peptidase 4"[MeSH Terms] OR "dipeptidyl peptidase 4"[All Fields] OR ("dipeptidyl"[All Fields] AND "peptidase"[All Fields] AND "iv"[All Fields]) OR "dipeptidyl peptidase iv"[All Fields])) AND ("renal insufficiency"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields]) OR "renal insufficiency"[All Fields] OR ("renal"[All Fields] AND "impairment"[All Fields]) OR "renal impairment"[All Fields]). The searches were limited to human subjects, and no language restriction was imposed. We did not include abstracts or meeting proceedings. In addition, we also searched the reference lists of the included studies and reviews to identify other potentially eligible papers that we may leave out of our primary search.

Study Selection

We included full-text publications when the following inclusion criteria were met: (1) study design: RCT; (2) study population: patients diagnosed with T2DM and had RI; (3) intervention: DPP-4 inhibitors; (4) comparison: placebo, or other glucose-lowering medications; (5) outcome measures: change from baseline in HbA1c, responder rates: achieving an HbA1c of <7%, fasting plasma glucose (FPG), adverse events; (6) sample size: more than 50.

Data Extraction

Two independent investigators extracted the following information from each trial: first author's name, year of publication, country of origin, sample size in each group, patients' characteristics, methods of randomization and blind, duration of follow-up, the change from baseline in HbA1c, FPG, prevalence of adverse events. When the same population appeared in several publications, we only included the most informative study to avoid duplication of information. Any discrepancies were resolved by discussion and consensus.

Risk of Bias and Evidence of Grade Assessment

The risk of bias in RCTs was assessed using the method recommended by Cochrane Collaboration[13]. The scale consists of seven items describing random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias[13]. Each study was classified as "high", "unclear", or "low" risk of bias[13].

The quality of evidence for outcome measures was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[14]. Through reviewing the inconsistency, indirectness, imprecision, and publication bias, each outcome was regarded as very low, low, moderate, or high quality[14]. A summary table was constructed using the GRADE profiler (GRADE pro, version 3.6).

Statistical Analysis

We calculated weight mean difference (WMD) with 95% confidence intervals (95%CIs) for continuous outcomes, and risk ratio (RR) with 95%CIs for dichotomous outcomes. Before the data were pooled, we used the Cochrane Q chi-square test and I^2 statistic to test the heterogeneity across studies, in which p-value less than 0.1 or I^2>50% indicated significant heterogeneity[15]. A random-effects model (DerSimonian-Laird method)[16] was used to pool data when significant heterogeneity was identified; otherwise, a fixed-effects model (Mantel-Haenszel method)[17] was used. We also conducted sensitivity analysis, meta-regression, and subgroup analysis based on types of DPP-4 inhibitors, and severity of RI to explore the potential sources of heterogeneity whenever significant heterogeneity was present. Publication bias was assessed by the Begg's[18] and Egger's test[19]. A p-value less than 0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were performed using STATA, version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study Identification and Selection

The initial search yielded 1,327 relevant publications from the PubMed, Web of Science, and Embase. After removing duplicates and screening titles/abstracts, 759 articles were thought to be potentially eligible for inclusion. After reviewing the full-text information, four were excluded as the following reasons: one was a sing-arm study[20], two trials compared two types of DPP-4 inhibitors (sitagliptin versus glipizide, or sitagliptin versus vildagliptin)[21,22], one reported other outcomes out of our interest[23]. Finally, 13 RCTs[24-36] met the inclusion criteria and were included in this investigation. The flow chart of literature search is shown in Figure 1.

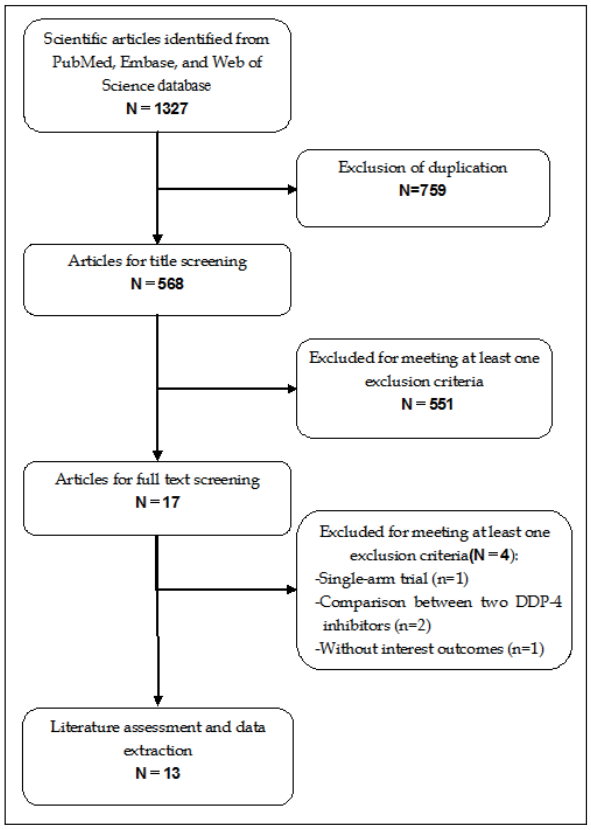

Figure 1. Eligibility of studies for inclusion in meta-analysis.

Study Characteristics

The main characteristics of the included trials were summarized in Table I. These trials were published from 2008 to 2017. Population sizes ranged from 51 to 575, with a total of 2,940 patients. Among the included studies, 4 of 13 compared linagliptin with placebo[24,25,29,33], four compared vildagliptin with placebo[27,28,31,34], one compared gemigliptin with placebo[30], one compared sitagliptin with placebo[26], one compared sitagliptin with glipizide[32], and two compared saxagliptin with placebo[35,36]. Among the 13 RCTs, all reported moderate to severe RI patients[24-36], three reported only severe RI patients[27-29], and three additionally reported end-stage renal disease patients[32,35,36].

Risk of Bias Assessment and Quality Assessment

The details of risk bias are summarized in Figure 2. Overall, seven trials were classified as being at low risk of bias, and six as being at unclear risk of bias. An adequate randomized sequence

Table I. Baseline characteristics of patients in the trials included in the meta-analysis.

Study	Country	Treatment regimen	No. of patients	Age (mean ± SD, y)	Duration of T2DM (mean± SD, y)	HbA1c (mean± SD, %)	BMI (mean± SD, kg/m^2)
Laakso M[24]	Finland	Linagliptin	113	66.6±9.3	NR	8.1±0.9	NR
		Placebo	122	66.6± 9.3	NR	8.1±0.9	NR
McGill JB[25]	USA	Linagliptin	58	69.3 ±10.2	NR	8.2±1.1	31.1±5.3
		Placebo	33	70.2±8.3	NR	8.1±0.6	30.3±5.2
Chan JC[26]	China	Sitagliptin	65	68.9±9.8	13.6 ± 9.7	7.6 ± 0.9	26.5 ±4.0
		placebo	26	65.3 ± 9.7	13.2 ± 8.9	7.8± 0.9	26.9± 4.5
Lukashevich V[27]	USA	Vildagliptin	100	64.1 ± 9.0	18.8 ± 8.3	NR	30.8 ± 5.8
		Placebo	78	64.9 ± 11.3	20.2 ± 9.5	NR	29.6 ± 5.0
Ito M[28]	Japan	Vildagliptin	30	67±2	NR	6.7±0.1	22.7±0.5
		Placebo	21	68±2	NR	6.7±0.1	22.4±0.5
McGill JB[29]	USA	Linagliptin	68	64.0 ±10.9	NR	8.2±1.1	32.3±5.8
		Placebo	65	64.9±9.6	NR	8.2±0.9	31.7±5.9
Yoon SA[30]	Korea	Gemigliptin	64	62.3±9.0	15.9±8.7	8.4±1.0	26.5±4.3
		Placebo	66	61.7±7.9	16.7±9.0	8.3±0.9	26.0±3.7
Kothny W[31]	Finland	Vildagliptin	216	67.1±9.0	15.9±9.2	7.9±1.0	30.3±5.2
		Placebo	153	69.3±7.2	15.2±9.8	7.9±1.0	30.1±5.0
Arjona Ferreira JC[32]	USA	Sitagliptin	64	60.5±9.1	19 [12-24]	7.9±0.7	27.3±5.7
		Glipizide	65	58.5±9.9	16 [11-23]	7.8±0.7	26.3±4.3
McGill JB[33]	Germany	Linagliptin	346	62.4±9.2	NR	8.3±0.8	30.7±5.0
		Placebo	338	62.7±8.6	NR	8.2±0.8	31.1±5.0
Lukashevich V[34]	USA	Vildagliptin	289	67.7±8.8	15.0±9.1	7.8±1.0	30.2 ± 5.1
		Placebo	226	69.7±7.3	15.2 ± 10.0	7.8±0.9	30.0±5.0
Nowicki M[35]	Poland	Saxagliptin	81	67	>10 years	8.5%	NR
		Placebo	83	67	>10 years	8.1%	NR
Nowicki M[36]	Poland	Saxagliptin	85	66.8±8.3	15.1±7.5	8.5±1.2	31.2±6.1
		Placebo	85	66.2±9.1	18.2±8.5	8.1±1.1	30.2±6.8

Abbreviation: SD, standard deviation; T2DM, type 2 diabetes Mellitus; BMI, body mass index; HbA1c, hemoglobin A1c; NR, not reported.

was generated in 12 trials[24-28,30-36], allocation sequence concealment was adequately reported in 9 trials[24,25,28,29,32-36], and blinding of participants and personnel were reported in 12 trials[24-27,29-36]. The other four items were reported in all trials.

The GRADE evidence profiles for these outcomes were shown in Table II. The quality of evidence was high for response rate, body-weight, and adverse events, and moderate for change from baseline in HbA1c, FPG, and hypoglycemia.

Change from Baseline in HbA1c

All the included studies reported the data of HbA1c[24-36]. The aggregated results of these reports suggested that the change from baseline in HbA1c was significantly greater in the DPP-4 inhibitor group than that in the control group (WMD=-0.50, 95%CI: -0.61, -0.39; p<0.001) (Figure 3). There was substantial heterogeneity among the included studies (I^2=98.1%, p<0.001).

Subgroup analysis based on the types of DPP-4 inhibitors showed that, all these regimens were associated with more change from baseline in HbA1c compared with placebo (linagliptin: WMD=-0.45, 95%CI: -0.64, -0.25, p<0.001;sitagliptin: WMD=-0.40, 95%CI: -0.56, -0.24, p<0.001; vildagliptin: WMD=-0.66, 95%CI: -0.81, -0.51, p<0.001; gemigliptin: WMD=-0.80, 95%CI: -0.98, -0.61, p<0.001;saxagliptin: WMD=-0.43, 95%CI: -0.76, -0.11, p<0.001); whereas sitagliptin had similar effect in HbA1c with glipizide (WMD=-0.07, 95%CI: -0.40, 0.26, p=0.669).

Subgroup analysis based on severity of RI demonstrated that, HbA1c level was significantly reduced in moderate (WMD=-0.69, 95%CI: -0.87, -0.52; p<0.001) and severe RI (WMD=-0.55, 95%CI: -0.68, -0.42; p<0.001) patients, but not in those with end-stage renal disease (WMD=-0.03, 95%CI: -0.18, 0.12; p=0.682) (Figure 4).

Fasting Plasma Glucose

Eleven RCTs reported the data of fasting plasma glucose[24-27,29-32,34-36]. Pooled estimates showed that DPP-4 inhibitors were associated with a similar change from baseline in FPG with

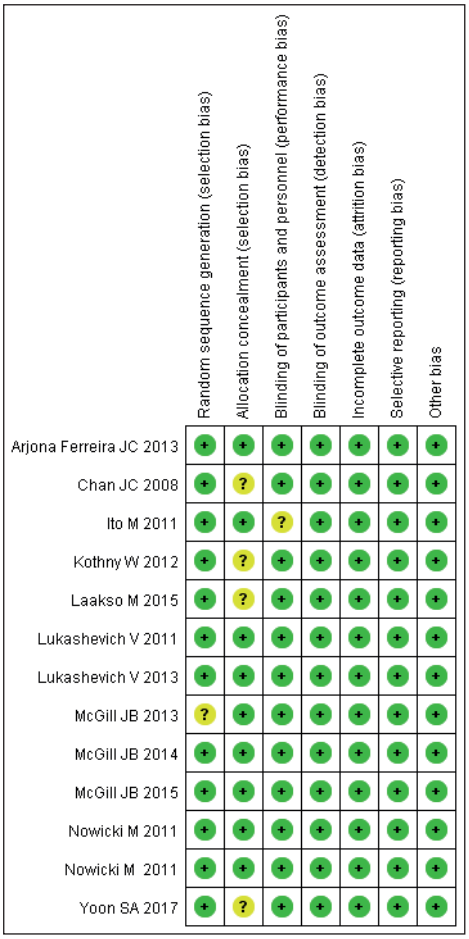

Figure 2. Risk of bias summary.

other treatments (WMD=-0.36, 95%CI: -0.92, 0.20; p=0.204) (Figure 5). Substantial heterogeneity was identified across the included studies (I^2=97.1%, p<0.001).

Subgroup analysis based on the types of DPP-4 inhibitors showed that, all these regimens except gemigliptin were associated with comparable change from baseline in FPG with placebo (linagliptin: WMD=-0.14, 95%CI: -0.38, 0.10, p=0.26; sitagliptin: WMD=0.30, 95%CI: -0.29, 0.89, p=0.316; vildagliptin: WMD=-0.94, 95%CI: -2.10, 0.21, p=0.123; saxagliptin: WMD=0.11, 95%CI: -0.65, 0.87, p=0.189; gemigliptin: WMD=-1.60, 95%CI: -1.78, -1.42, p<0.001). Sitagliptin had similar effect in FPG with glipizide (WMD=0.25, 95%CI: -0.65, 1.15, p=0.586) (Figure 5).

Subgroup analysis based on severity of RI demonstrated that, FPG level was significantly reduced in moderate (WMD=-0.55, 95%CI: -0.73, -0.36; p=0.028) and severe RI patients (WMD=-0.91, 95%CI: -1.71, -0.10; p<0.001), but not in those with end-stage renal disease (WMD=1.33, 95%CI: -0.78, 3.44; p=0.216) (Figure 6).

Responder Rates: Achieving an HbA1c of <7%

Three RCTs reported the data of response rate[27,31,34]. The response rate in the DPP-4 inhibitor group and control group was 35.1% and 25%, respectively. Pooled estimates suggested that DPP-4 inhibitors were associated with a significantly higher response rate than other treatment (RR=1.38, 95%CI: 1.12, 1.70; p=0.002). There was no significant heterogeneity among the included studies (I^2=16.8%, p=0.301).

Body-weight

Eight RCTs reported the data of body-weight[25-30,33,36]. Pooled results showed that DPP-D4 inhibitors had a similar change in body weight with placebo (WMD=-0.72, 95%CI: -1.44, -0.01; p=0.053). There was moderate heterogeneity among the included studies (I^2=46.8%, p=0.047).

Hypoglycemia

Nine RCTs reported the data on hypoglycemia[24,25,27,29-32,34,35]. There were 259 out of 925 (28%) patients in the DPP-4 inhibitor group and 200 out of 870 (23.0%) patients in the control group that experienced hypoglycemia. Pooled estimates showed that, compared with control, DPP-4 inhibitors did not increase the risk of hypoglycemia (RR=1.31, 95%CI: 0.97, 1.77; p=0.075). There was significant heterogeneity among the included studies (I^2=64.7%, p=0.004).

Adverse Events

All trials provided data on adverse events[24-36]. Compared with control, DPP-4 inhibitors were associated with comparable prevalence of adverse events (RR=0.98, 95%CI: 0.94, 1.02; p=0.256), serious adverse events (RR=1.02, 95%CI: 0.88, 1.20; p=0.773), drug related adverse events (RR=0.86, 95%CI: 0.73, 1.01; p=0.074), discontinuation due to an adverse event (RR=0.96, 95%CI: 0.74, 1.25; p=0.757), and mortality (RR=1.12, 95%CI: 0.64, 1.97; p=0.689).

Sensitivity Analysis

Since there was substantial heterogeneity for HbA1c and FPG among the included studies, we therefore conducted sensitivity analysis based on different criteria. The results of sensitivity analysis were presented in Table III. The overall estimates for treatment effects in HbA1c and FPG changed little in the sensitivity analysis.

Table II. GRADE evidence profile.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
Change from baseline in HbA1c (Better indicated by lower values)												
13	Randomized trials	No serious risk of bias[1]	Very serious[1]	No serious indirectness	No serious imprecision	Strong association[2]	1579	1361	–	WMD-0.50 lower (-0.61 higher to -0.39 lower)	⊕⊕⊕O MODERATE	CRITICAL
Fasting plasma glucose (Better indicated by lower values)												
11	Randomized trials	No serious risk of bias	Very serious[3]	No serious indirectness	No serious imprecision	Strong association[4]	1171	1009	–	WMD -0.36 lower (-0.92 to 0.20 higher)	⊕⊕⊕O MODERATE	CRITICAL
Responder rates: achieving an HbA1c of <7%												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	167/476 (35.1%)	109/436 (25%) 24.8%	RR 1.38 (1.12 to 1.70)	95 more per 1000 (from 30 more to 175 more) 94 more per 1000 (from 30 more to 174 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Bodyweight (Better indicated by lower values)												
8 trials	Randomized risk of bias	No serious inconsi-	No serious indirectness stency	No serious	No serious imprecision	None	572	491	–	WMD -0.72 lower (-1.44 higher to -0.01 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Hypoglycemia												
9	Randomized trials	No serious risk of bias	Serious[5]	No serious indirectness	No serious imprecision	None	259/925 (28%)	200/870 (23%) 11.9%	RR 1.31 (0.97 to 1.77)	71 more per 1000 (from 7 fewer to 177 more) 37 more per 1000 (from 4 fewer to 92 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events												
13	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1182/ 1527 (77.4%)	1026/ 1325 (77.4%) 75.8%	RR 0.98 (0.94 to 1.02)	15 fewer per 1000 (from 46 fewer to 15 more) 15 fewer per 1000 (from 45 fewer to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

1 Substantial heterogeneity (I2 =98.1%) was found; 2 A total of 2,940 patients were enrolled; 3 Substantial heterogeneity (I2 =97.1%) was found; 4 A total of 2,180 patients were enrolled; 5 Moderate heterogeneity (I2 =64.7%) was found

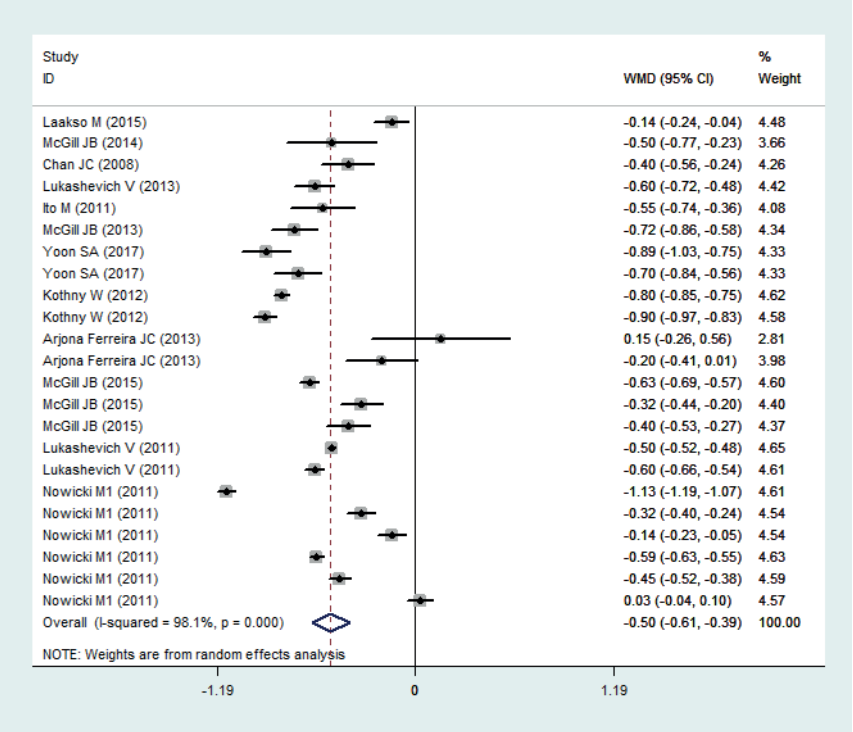

Figure 3. Forest plot showing the effect of DPP-4 inhibitors on HbA1c.

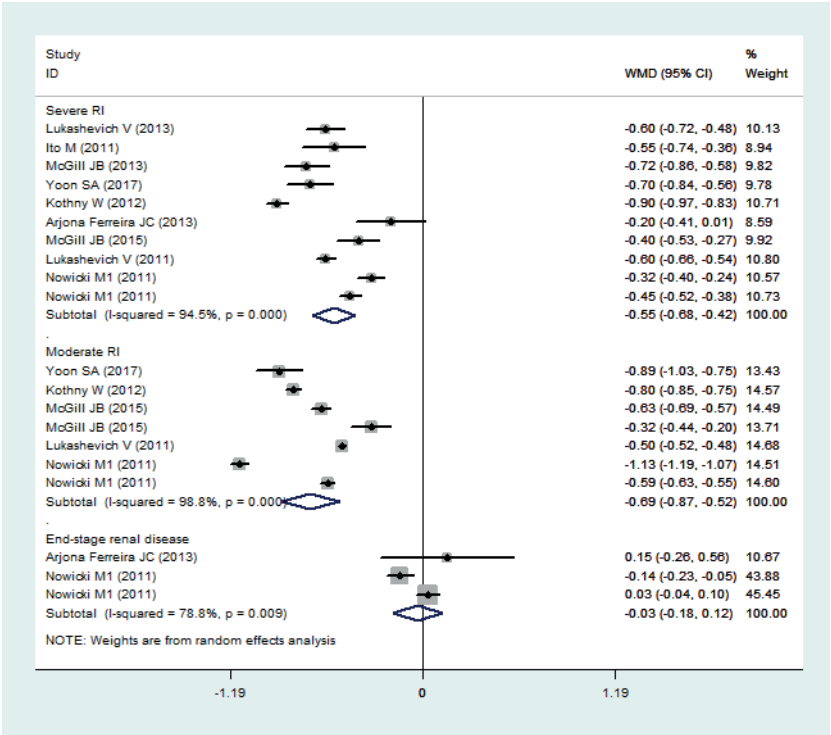

Figure 4. Forest plot showing subgroup analysis based on severity of RI for DPP-4 inhibitors on HbA1c.

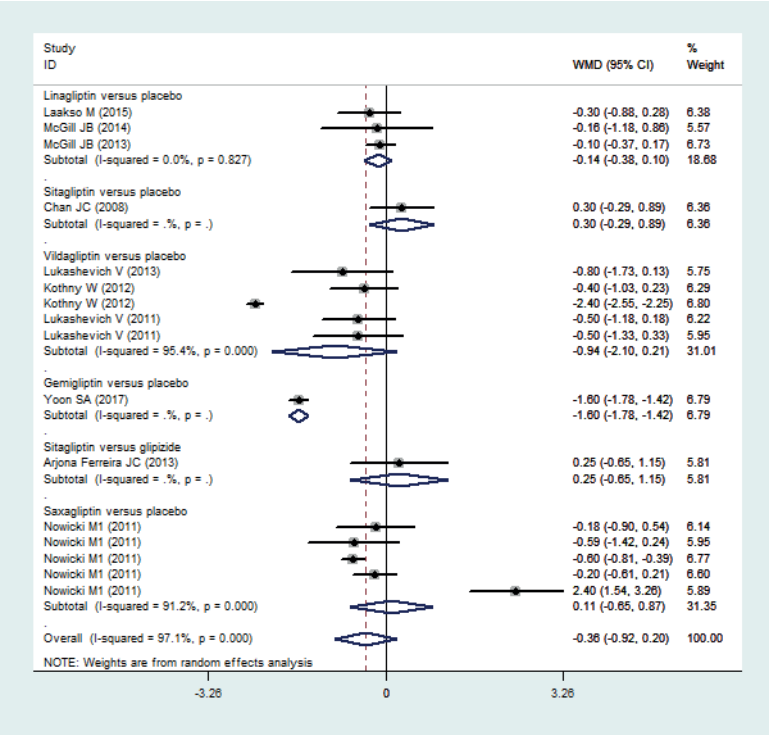

Figure 5. Forest plot showing the effect of DPP-4 inhibitors on FPG.

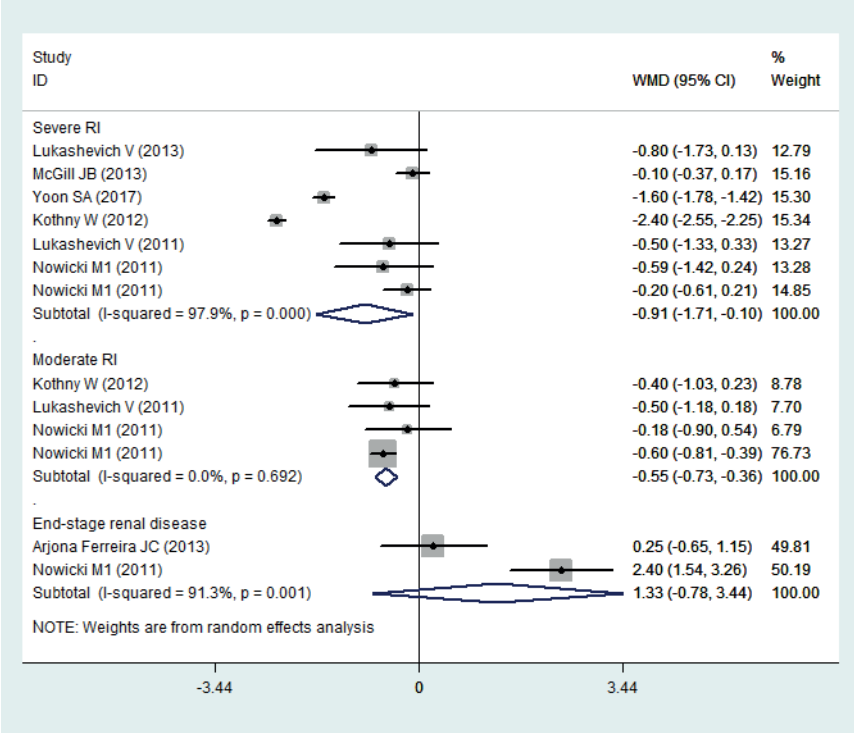

Figure 6. Forest plot showing subgroup analysis based on severity of RI for DPP-4 inhibitors on FPG.

Meta-regression

We first conducted univariate meta-regression analyses for each of the following variables: types of DPP-4 inhibitors, severity of RI, sample size, and duration of intervention. There was no significant association of effect size with these variables for the change in HbA1c level (types of DPP-4 inhibitors, p=0.692; severity of RI, P=0.144; sample size, p=0.641; duration of intervention, p=0.444) and FPG (types of DPP-4 inhibitors, p=0.515; severity of RI, p=0.699; sample size, p=0.673; duration of intervention, p=0.891).This indicated that these variables were not significant and independent predictors for heterogeneity, strengthening the results of the present subgroup analysis.

Publication Bias

Assessment of publication bias was conducted by Egger's and Begg test, and results showed that no publication bias existed among the included studies (Egger's test: t=-0.15, p=0.885; Begg test: Z=0.25, p=0.806).

Discussion

This is a further meta-analysis to evaluate the effects and safety of DPP-4 inhibitors in the treatment of T2DM patients with moderate or severe RI. The present meta-analysis of 13 RCTs showed that compared with other treatments, DPP-4 inhibitors were associated with significantly greater change in HbA1c level, and a higher response rate of patients achieving the HbA1c goal of <7%. Subgroup analysis suggested that the beneficial effect of DPP-4 inhibitors in HbA1c were observed in all types of DPP-4 inhibitors, and in patients with moderate or severe RI, but not in those with end-stage renal disease. DPP-4 inhibitors did not significantly lower the FPG level, and this was seen in all types of DPP-4 inhibitors except gemigliptin. The prevalence of adverse events in DPP-4 inhibitors and control groups were not significantly different, and DPP-4 inhibitors did not induce a higher rate of hypoglycemia than other treatment.

There have been two published systematic review and meta-analysis of DPP-4 inhibitors in the treatment of T2DM patients with moderate or severe RI[10,11]. Both of them showed that the use of DPP-4 inhibitors was associated with significant reduction in HbA1c. Our meta-analysis expands on these two earlier meta-analyses to provide a better characterization of the evidence base for the use of DPP-4 inhibitors in T2DM patients with moderate or severe RI. First, the present meta-analysis had more enlarged sample sizes than the previous analysis, giving greater power to assess the effects. In this meta-analysis, we included 13 RCTs with a total number of 2,940 patients, and all these trials were prospective, randomized placebo-controlled trials. Whereas, in the previous studies, the number of included RCTs was only five (503 patients) and ten (1,915 patients). Second, in this meta-analysis, all the included trials were published articles with full-data; whereas in the work conducted by Cheng et al[11], half of the studies were published in the form of conferences abstracts, clinical trials registries, company websites, and FDA and EMA websites, without access to the full-data. Articles without complete outcome data might have an overestimated treatment effect. Third, in this meta-analysis, we further conducted subgroup analysis based on different types of DPP-4 inhibitors and severity of RI, which had not been investigated in the previous meta-analysis. Fourth, in this meta-analysis, we performed meta-regression to explore the potential sources of heterogeneity, and results showed that the variables were not significant and independent predictors for heterogeneity, which strengthened the results of the subgroup analysis. Fifth, in the study conducted by Cheng et al[11], publication bias was identified, which reduced the precise and reliable effect estimates.

In this meta-analysis, DPP-4 inhibitors were associated with a significant reduction in HbA1c levels in T2DM patients with moderate to severe RI. Also, we noted that the reduced HbA1c levels were clear across all types of DPP-4 inhibitors. Our results were in consistent with the findings of the previous studies. The mean change from baseline in HbA1c ranged from -0.72% to -0.14% for linagliptin[24,25,29,33], -0.90% to -0.50% for vildagliptin[27,28,31,34], -0.89% to -0.70% for gemigliptin[30], and -1.13% to -0.14% for saxagliptin[35,36], as compared with placebo. In the subgroup analysis of patients with different severity of RI, a significant reduction in HbA1c level was seen in patients with moderate and severe RI, but not in those with end-stage renal disease.

Among the included trials, only three investigated the effects of DPP-4 inhibitors in end-stage renal disease patients[32,35,36], but all of them reported the negative results in this population. In the study conducted by Nowicki et al[35], T2DM patients were randomly assigned to receive saxagliptin 2.5 mg once daily or placebo. At the 52-week, the reduction in HbA1c levels was greater with

saxagliptin than placebo in patients with RI rated as moderate (-0.94% *vs.* 0.19%) or severe (-0.81% *vs.* -0.49%), but similar to placebo for those with end-stage renal disease (-1.13% *vs.* -0.99%)[35]. Similarly, in another randomized, double-blind trial that compared the effects of sitagliptin with glipizide in end-stage renal disease patients, although both reduced the HbA1c levels (-0.73% *vs.* -0.87), the difference between them was not significant (difference=0.15, 95%CI: -0.18, 0.49)[32]. It should be noted that the HbA1c levels can be falsely low in patients with end-stage renal disease subgroup because of uremia-induced changes in hemoglobin structure (e.g., carbamylation)[37]. The carbamylated hemoglobin can interfere with laboratory analysis of HbA1c levels, although the use of high-performance liquid chromatography standardized and aligned to the Diabetes Control and Complications Trial nearly eliminates this interference[37].

About FPG, our result suggested that DPP-4 inhibitors were associated with a similar reduction in FPG compared with other treatment. Our results were in line with the previous reports. However, in the subgroup analysis based on types of DPP-4 inhibitors, this negative result was seen clear across all regimens except gemigliptin, which reported a numerically greater decrease in FPG than placebo. In the GUARD study[30], 132 patients were randomized to receive gemigliptin or placebo. At Week 12, the mean reduction in FPG with gemigliptin was -10.06±9.72 mg/dL, whereas it was 18.69±9.57 mg/dL with placebo[30]. The between-group difference was significant (mean difference: -28.75mg/dL, 95%CI: -51.17, -6.33 mg/dL)[30]. However, since there was only one trial reporting the effect of gemigliptin in FPG, the evidence might not be robust. More large-scale RCTs are needed to investigate the effect of gemigliptin in reducing the FPG level.

Despite DPP-4 inhibitors showed no beneficial effect in FPG, subgroup analysis showed a greater reduction of DPP-4 inhibitors in patients with moderate and severe RI, but not in those with end-stage renal disease. The effect of DPP-4 inhibitors in FPG remained inconsistent among the included trials. Of the seven trials that reported the data of DPP-4 inhibitors in severe RI patients, only two showed that DPP-4 inhibitors were associated with a greater decrease in FPG than placebo[30,31]. In the trial of Kothny et al[31], T2DM patients were treated with vildagliptin or placebo. After 1 year, the mean FPG in severe RI patients decreased by 1.8±0.5 mmol/l in vildagliptin group compared with 0.6±0.4 mmol/l in placebo group[31]. The between group difference was significant (mean difference=-1.2±0.4 mmol/l, p=0.008)[31]. However, this difference was not observed in moderate RI patients. Among the studies that reported the data for moderate RI patients, only one suggested that saxagliptin significantly reduced the FPG level compared with placebo[36]. In that study, 44 and 40 patients with moderate RI were randomly selected to receive saxagliptin or placebo. At 12-week, the change from baseline in FPG in the two groups was -0.8±0.5 mmol/l and -0.2±0.5 mmol/l, respectively[36]. Saxagliptin resulted in a greater decrease in FPG than placebo (mean difference: -0.7±0.7 mmol/l)[36]. Since the sample size of moderate RI patients in that study was relatively small, the difference between the groups might be caused by the statistical error. Thus, more large-scale RCTs focusing on moderate RI patients are needed to validate the effects of DPP-4 inhibitors in this population.

A general treatment goal for patients with T2DM is to achieve glycemic control without causing hypoglycemia or weight gain. In the current meta-analysis, patients who received DPP-4 inhibitors showed similar reduction in weight and had no higher rate of hypoglycemia than did those who received placebo or antihyperglycemic drugs. In our investigation, the percentage of patients who experienced hypoglycemia was comparable in DPP-4 inhibitor and control group (28% *vs.* 23.0%), which was in consistent with the conclusion from most of the published studies. Whereas, in the trial conducted by Lukashevich et al[34], there was a significantly higher rate of hypoglycemia with vildagliptin than placebo. In that study, 165 and 129 patients with moderate RI, and 124 and 97 patients with severe RI were randomly allocated to the vildagliptin and placebo group, respectively[34]. At 24-week, 17.2% of moderate RI patients receiving vildagliptin experienced hypoglycemia compared with11.6% of patients receiving placebo (p<0.001)[34]. Whereas, in patients with severe RI, the prevalence of hypoglycemia was similar the two groups (15.3% *vs.* 12.4%)[34]. Similarly, in another randomized, double-blind, 52-week trial that assessed the efficacy of vildagliptin[31], the rate of hypoglycemia was significantly higher in moderate RI patients (26.2% *vs.* 16.9%), and similar in severe RI patients (18.1% *vs.* 17.2%)[31]. The authors suggested that many factors might contribute to hypoglycemia in vildagliptin-treated patients, including the insulin treatment at study entry, and the better

glycemic control of vildagliptin than placebo[31]. Indeed, there is even evidence of a potential protective effect of vildagliptin against insulin-induced hypoglycemia. When vildagliptin was added to insulin therapy in patients with normal RI, the hypoglycemia was less frequently seen in patients treated with vildagliptin than those receiving placebo, in spite of better glycemic control[38,39]. Christensen et al[40] presented a mechanistic explanation for the putative protective effect of vildagliptin, which might be explained by the increases in gastric inhibitory peptide-mediated stimulation of glucagon release during incipient hypoglycemia, as has been shown with hyperinsulinaemic clamps[41].

The results of this meta-analysis must be interpreted with caution in light of the limitations of the included trials. First, there was substantial heterogeneity between studies in the overall analysis, which was not surprising given the differences in characteristics of population, types of DPP-4 inhibitors, duration of intervention, and CKD stage. These factors may result in the heterogeneity and have potential impact on our results. However, we have identified none of these factors accounting for inconsistency through a series of subgroup analysis, sensitivity analysis and meta-regression. Thus, the heterogeneity might be caused by the clinical treatment effect rather than the methodological differences. Second, among the included trials, three had a relatively small sample size (N<100). Despite most of the included studies were classified as being at low risk of bias, caution should be taken when interpreting the results because small trials were highly subject to overestimate the treatment effect compared with larger trials. Third, it should be noted that all the included trials were sponsored by pharmaceutical companies, and their results might have been affected by the inherent conflict of interest and possible bias.

Conclusions

The present meta-analysis showed that DPP-4 inhibitors significantly reduced the HbA1c levels in T2DM patients with moderate to severe RI. And the treatment of DPP-4 inhibitors did not increase the risk of hypoglycemia and adverse events. Our study further demonstrated that DPP-4 inhibitors were effective and well tolerated by patients with moderate to severe RI. However, for patients with end-stage renal disease, DPP-4 inhibitors appeared to have no beneficial effect in this population. Considering the potential limitations in this meta-analysis, more large-scale, well-conducted RCTs are needed to identify our findings.

Conflict of Interest

The authors declare that they have no conflict of interests.

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