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Original Article

Efficacy and safety of sitagliptin in patients with type 2 diabetes mellitus: a meta-analysis

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Abstract: Backround: Several dipeptidyl peptidase IV (DPP-IV) inhibitors have been developed and commonly used. However, healthcare providers question that which one is superior over the other for both hypoglycemic efficacy and safety as very few comparison trials have been conducted so far. The aim of this systematic review was to evaluate the hypoglycemic efficacy and safety of sitagliptin with other DPP-IV inhibitors directly in patients with type 2 diabetes mellitus. Material and method: We conducted a systematic review of English articles using database of Pubmed, Embase, Cochrane library, Sinomed and clinical trial register centers, for randomized controlled trials of DPP-IV inhibitors in patients with type 2 diabetes mellitus. Two authors extracted the articles independently. A meta-analysis was performed when homogeneous enough. Results: Four studies, including 6 comparisons (2 for sitagliptin vs. saxagliptin, 2 for sitagliptin vs. vildagliptin and 2 for sitagliptin vs. gemigliptin) were included in this meta-analysis. HbA1c was analyzed, and there was no statistical difference between sitagliptin and three other agents in total (mean difference -0.09, 95% CI, -0.17 to -0.00). Pooled data of total side effects did not find any statistical difference in total and when compared to other side effects. However, two studies reported the side effect of arthralgia, and one showed that the incidence of arthralgia was higher in sitagliptin than saxagliptin. Conclusions: All the four agents of DPP-IV inhibitors have good efficacy and safety. Sitagliptin was not superior to other three DPP-IV inhibitors (saxagliptin, vildagliptin, and gemigliptin).

Keywords: Dipeptidyl-peptidase IV inhibitors, meta-analysis, randomized controlled trial, diabetes mellitus, type 2

Introduction

Dipeptidyl peptidase IV (DPP-IV) inhibitors are a new class of oral hypoglycemic agents that acts by blocking the degradation of glucagon-like peptide-1 (GLP-1) and improve glycemic control [1]. This class has the advantage of fewer side effects and fewer incidences of hypoglycemic events [2-5]. It was stated previously that DPP-IV inhibitors have been considered as second line of drugs for the management of hyperglycemia in type 2 diabetes mellitus (T2DM) in clinical guidelines both domestic and overseas [6, 7]. Members of this class can be used as an adjunct drug with metformin, sulfonylurea, insulin and other first line medication. DPP-IV inhibitors also have been authorized for utilizationin those patients with intolerance or contraindication to metformin or sulfonylurea, as well as diabetic patients with chronic renal insufficiency [8].

Several DPP-IV inhibitors, including sitagliptin, saxagliptin, vildagliptin, gemigliptin, linagliptin, and alogliptin, have been developed and commonly used in clinical settings. The pharmacokinetic and pharmacodynamic differences present in different types of DPP-IV inhibitors influence the clinical efficacy and safety in patients with T2DM [9-12]. New types of DPP-IV inhibitors are being developed continuously. At the same time, it often interested healthcare providers as to which agent has better efficacy and safety. Review of clinical trials, especially randomized controlled trials (RCTs), might be the answer. However, very few clinical trials have been conducted to show comparison of the efficacy and safety of different DPP-IV inhibitors. Current evidence which had been published compared sitagliptin with three other different DPP-IV inhibitors. Due to limited available data, it was unclear whether sitagliptin had better glycemic control, and fewer side effects than

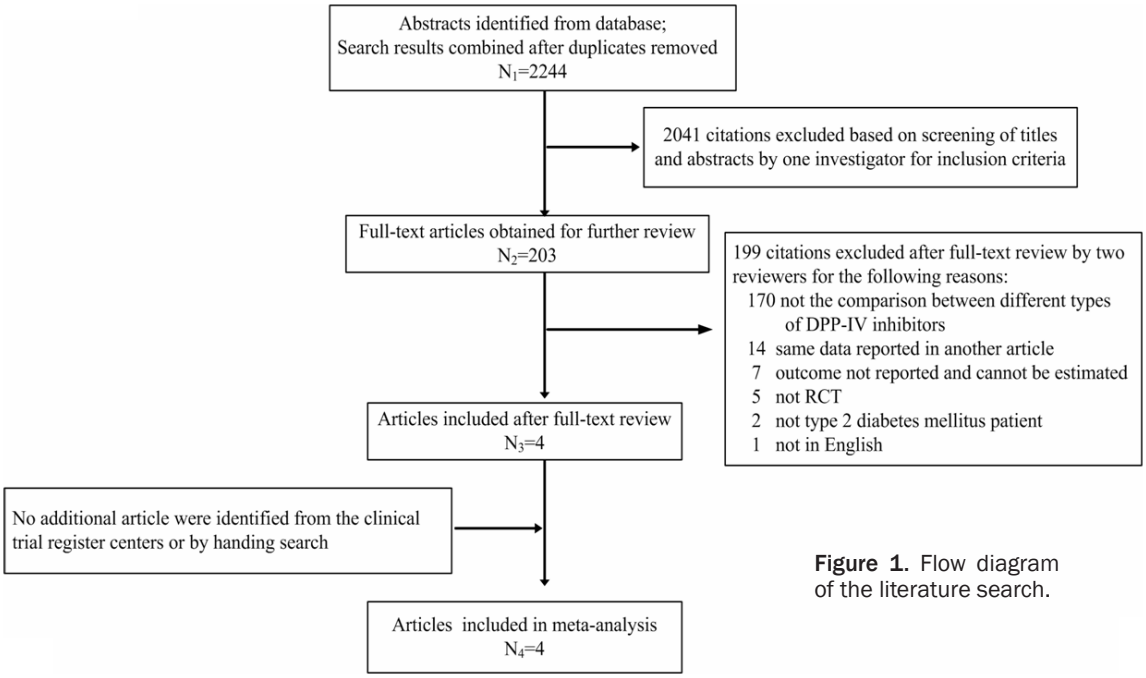

Figure 1. Flow diagram of the literature search.

other. To evaluate the efficacy and safety, we conducted a systematic review with meta-analysis to compare sitagliptin with three other DPP-IV inhibitors that can provide a reference for clinical choice.

Materials and methods

Search criteria

A search of the following databases: PubMed, Embase, Cochrane library and Sinomed for RCTs of dipeptidyl peptidase IV inhibitors in patients with type 2 diabetes mellitus was conducted. Additional trials at the clinical trial register centers (http://www.clinicaltrials.gov) were also searched. Dipeptidyl peptidase IV inhibitors and RCT were used as keywords or mesh term to search for the earliest data to 1 May 2015. References to all eligible articles and previous related reviews were hand searched. Clinical trials that met the following criteria: (i) published in English, (ii) RCT design, (iii) included patients with type 2 diabetes at least 18 years old without pregnancy, (iv) primary study comparing at least two different DPP-IV inhibitors, (v) at least 12 weeks follow-up, (vi) at least one baseline and post-treatment of hypoglycemic efficacy (including HbA1c, fasting plasma glucose (FPG) or 2-h postprandial plasma glucose (P2hG)) and/or safety outcome were considered.

Study selection and data extraction

Two reviewers screened the abstracts and extracted data from included studies using data extraction sheet, independently. They screened the paper in duplicate and discussed among themselves to resolve any disagreements. The third reviewer would decide if an agreement could not be reached. Information extracted included: (i) general characteristics of studies (including first authors' name, year of publication, and sample size in each group) and the inclusion criteria, (ii) type of intervention (including type, dosage and duration), (iii) type of outcome and measurement.

Statistical analysis

The primary endpoint was the change of HbA1c, FPG and P2hG from baseline. The side effects of different drugs were also analyzed. The meta-analysis with the fixed effects model was performed by computing the mean difference (MD) or standard mean difference (SMD) and 95% CI for outcomes of continuous variables. Odds ratio (OR) and 95% CI were used for dichotomous variables. The statistical analysis method used in the current study for each analysis was Mantel-Haenszel method. I^2 was calculated as an index of heterogeneity between studies. The degree of heterogeneity was divided by the l evel of I^2 as following: 0-25%, no het-

Table 1. Characteristics of randomized controlled trials included in the meta-analysis

Author, year	Intervention		Number of participants (n)		Average duration of diabetes (years)		Average age (year)		Women (%)		Baseline HbA1c (%)		Follow-up (weeks)
	Drug A	Drug B	Drug A	Drug B	Drug A	Drug B	Drug A	Drug B	Drug A	Drug B	Drug A	Drug B	
Scheen et al., 2010	Sitagliptin 100 mg qd	Saxagliptin 5 mg qd	398	403	6.3	6.3	58.1	58.8	49.2	52.9	7.7	7.7	18
Li et al., 2014 [1]	Sitagliptin 100 mg qd	Saxagliptin 5 mg qd	34	71	-	-	48.6	46.5	46	41	8.54	8.86	24
Li et al., 2014 [2]	Sitagliptin 100 mg qd	Vildagliptin 50 mg bid	34	69	-	-	48.6	44.8	46	41	8.54	8.75	24
Rizzo et al., 2012	Sitagliptin 100 mg qd	Vildagliptin 50 mg bid	45	45	8.6	8.9	60	60	55.6	48.9	8.5	8.2	12
Rhee et al., 2013 [1]	Sitagliptin 100 mg qd	Gemigliptin 25 mg bid	71	141	6.4	6.33	52.94	51.88	46.62	50	8.05	8.07	24
Rhee et al., 2013 [2]	Sitagliptin 100 mg qd	Gemigliptin 50 mg qd	71	142	6.4	6.14	52.94	53.99	46.62	40	8.05	7.93	24

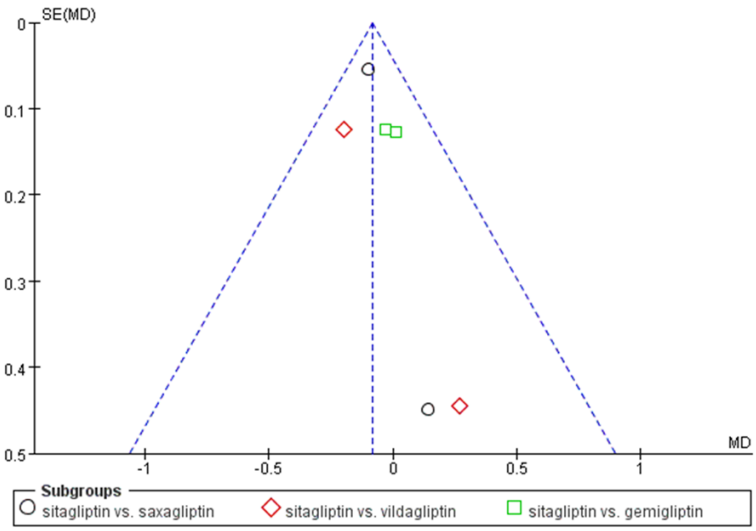

Figure 2. Funnel plots of the primary outcome.

erogeneity; 25-50%, moderate heterogeneity; 50-75%, large heterogeneity; 75-100%, extreme heterogeneity [13]. Subgroup analysis should be performed to find out the source of heterogeneity if I^2 were higher than 50%. If no heterogeneity exists, the fixed effects model was performed. Otherwise, the random-effects model was used.

Quality assessment and publication bias

Quality and bias risk were assessed via predefined categories: randomization, concealment of allocation, blind methods (participants and personnel, and outcome assessment), and extent of loss to follow-up. Two reviewers determined these items, independently. Funnel plots of the primary outcome by visual inspection was used to assess the potential publication bias [14]. This analysis was performed by using Review Manager 5.2 (Cochrane Collaboration, United Kingdom).

Results

Search results and study characteristics

The literature search found 2513 relevant articles and 2244 articles remained after duplication. Out of these, 203 were selected for full-text review. Finally, four articles met the inclusion criteria, and no additional article was identified from the clinical trial register centers or by any other search. The search progress was summarized in **Figure 1**. Four articles including seven pairs of comparisons were included [15-18]. Among these, only one showed the comparison of saxagliptin with vildagliptin by Li et al. [18], and finally there were six comparisons that sitagliptin compared with three other different DPP-IV inhibitors (including saxagliptin, vildagliptin, and gemigliptin) included in this meta-analysis.

Patients in these trials were required to have been treated with metformin or metformin plus another traditional oral hypoglycemic agents and be on a stable dose for at least 8 or 12 weeks. Similar mean age, the average duration of diabetes, sexual ratio and baseline HbA1c were provided in the six comparative groups (n=1524). Four DPP-IV inhibitors with recommended doses were applied (sitagliptin 100 mg qd, saxagliptin 5 mg qd, vildagliptin 50 mg bid, gemigliptin 25 mg bid or 50 mg qd) to compare the hypoglycemic efficacy and safety. The general characteristics of the six trials are summarized in **Table 1**.

Methodological quality

All of the four trials were randomized trials, however they were not detailed. None of these trials revealed the details of allocation concealment. Two of them were double-blinded trials [15, 16]. The withdrawal rates were less than 15% and were not significantly different between these comparative groups. The most common reasons for withdrawal were the loss of follow-up or side effects. Funnel plots of the primary outcome was showed in **Figure 2**. Shortly, the methodological quality of these studies in this meta-analysis was not good enough.

Efficacy

HbA1c: Neither statistical nor clinical difference were found in sitagliptin compared with other three DPP-IV inhibitors when pooled data from all six comparisons (MD, -0.09, 95% CI, -0.17 to -0.00). The heterogeneity among all comparisons was not significant (I^2=0). That meant hypoglycemic efficacy of sitagliptin was

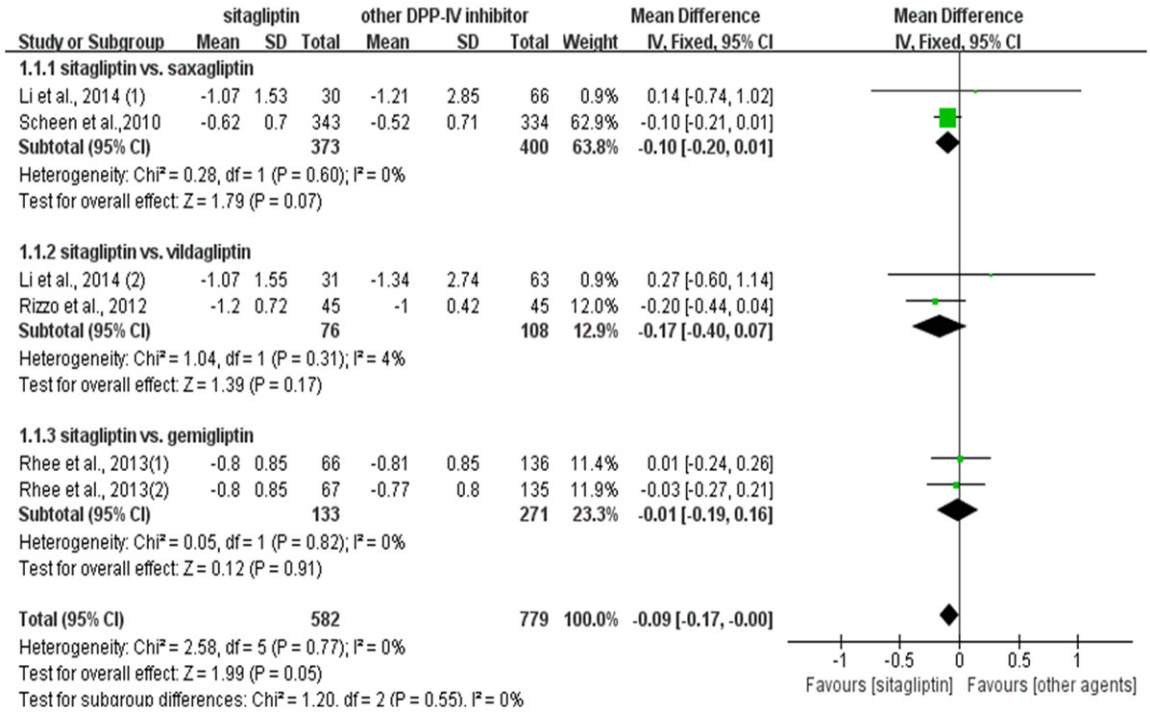

Figure 3. Change of HbA1c from baseline between sitagliptin and other DPP-IV inhibitors.

not better than the other three DPP-IV inhibitors in total. Further subgroup analyzes was conducted to compare sitagliptin with the other three DPP-IV inhibitors separately. No heterogeneity existed, and neither statistical nor clinical differences were found (**Figure 3**).

FPG and P2hG: All six comparisons reported FPG as a result in primary articles, and five had a result of P2hG. To summarize the data of FPG from all six studies with the fixed effects model showed a significant heterogeneity (I^2=61%). Therefore, the random effects model was conducted, and there was no statistical difference found in all six comparisons (SMD, -0.01, 95% CI, -0.21 to 0.19). Subgroup analysis by difference comparisons with sitagliptin was also conducted. It was found that either there was large heterogeneity (I^2: vs. saxagliptin, 79%; vs. gemigliptin, 83%) or no statistic difference at all when compared with gemigliptin (SMD, -0.09, 95% CI, -0.30 to 0.12). Same results of P2hG pooled with five comparisons were found but no significant difference was found. That meant both the declination of FPG and P2hG in patients treated with sitagliptin was not better than the other three drugs.

Safety

All the four articles reported side effects and the incidence of total side effects were not statistically different in total (OR, 0.98, 95% CI, 0.79 to 1.22) and each comparisons (sitagliptin vs. saxagliptin: OR, 1.01, 95% CI, 0.78 to 1.32; sitagliptin vs. vildagliptin: OR, 1.70, 95% CI, 0.72 to 3.99; sitagliptin vs. gemigliptin: OR 0.80, 95% CI, 0.53 to 1.20). That meant sitagliptin did not significantly increase the total side effects than other DPP-IV inhibitors. Subgroup analysis was conducted by different types of side effects, and the results were showed in **Table 2**. Headache, back pain, infection and gastrointestinal side effects were not associated with different DPP-IV inhibitors and no statistical differences existed. Hypoglycemia was the most common side effect that occurred in diabetic patients when hypoglycemic drug was used, however, there were no significant differences between sitagliptin and other DPP-IV inhibitors. Two studies reported the side effect of arthralgia [15, 16]. It was found that the incidence of arthralgia was higher in sitagliptin than saxagliptin (OR, 5.17, 95% CI, 1.13 to 23.74). Due to the limit sample size and study duration, future studies should pay more

Table 2. Pooled data of side effects between sitagliptin and other DPP-IV inhibitors

Side effects	Fixed effects model		Heterogeneity	
	OR [95% CI]	*P*	I^2 (%)	*P*
Ache				
Headache	0.89 [0.38, 2.08]	0.79	0	0.56
Back pain	0.93 [0.41, 2.09]	0.85	17	0.30
Arthralgia	3.38 [1.24, 9.19]	0.02	0	0.67
Infection				
Respiratory tract infection	0.87 [0.61, 1.23]	0.42	27	0.24
Urinary tract infection	0.92 [0.50, 1.69]	0.79	Not applicable	Not applicable
Hypoglycemia	0.92 [0.47, 1.82]	0.82	0	0.84
Gastrointestinal side effects	1.04 [0.67, 1.62]	0.85	0	0.58

attention to the side effect of arthralgia when DPP-IV inhibitor was used.

Discussion

The pooled data of the limited number of studies comparing directly different DPP-IV inhibitors did not define a superiority of one agent over the others. However, this meta-analysis indicated that all the four agents had hypoglycemic efficacy while sitagliptin was not superior to other three. So, the recommended choice of a DPP-IV inhibitor for patients with T2DM may be to focus on pharmacokinetic and pharmacodynamic differences, side effects, as well as drug cost and cost-effectiveness.

GLP-1 is one of the major incretins that can promote insulin secretion from β cell, and simultaneously inhibit the secretion of glucagon from α cell. Nevertheless, it is rapidly degraded and inactivated by DPP-IV. The inhibition of DPP-IV inhibitors can prevent the degradation of GLP-1 from DPP-IV, and, therefore, improve glycemic control. More and more different DPP-IV inhibitors have been developed and used. Sitagliptin, the first DPP-IV inhibitor approved by Food and Drug Administration (FDA) in the United States, has been suggested to be added to other traditional hypoglycemic agents [19]. One year later, another new DPP-IV inhibitor, vildagliptin, was approved by the European Union. As time goes on, more and more different DPP-IV inhibitors including saxagliptin, gemigliptin, linagliptin and so on, are developed and prescribed in clinical settings. Nowadays, gemigliptin is still not listed in China, and other three DPP-IV inhibitors have been used in clinical practise in recent years.

The half-life (T1/2) varies between DPP-IV inhibitors: 2-3 h for vildagliptin, 2.2-3.8 h for saxagliptin, 8-14 h for sitagliptin and 17-21 h for gemigliptin [20, 21]. The oral bioavailability and half maximal inhibitory concentration (IC50) in vitro are different as well. Sitagliptin, vildagliptin, and saxagliptin are all mainly excreted by the kidney [20]. DPP-IV inhibitors are divided into peptidomimetics and non-peptidomimetics due to their different chemical structures [22]. CYP enzyme is associated with the metabolism of DPP-IV inhibitors. Among these, saxagliptin is primarily metabolized by CYP3A4/5, and its metabolic product still has activity. Sitagliptin associated both with CYP3A4 and CYP2C8, gemigliptin associated with CYP3A4, but only 1% vildagliptin is associated with enzyme of CYP [23].

These pharmacokinetic and pharmacodynamic differences partly explain the different dose frequency and a daily therapeutic dose of DPP-IV inhibitors. Except that vildagliptin should be given twice daily with the dose of 100 mg per day, sitagliptin (100 mg/day) and saxagliptin (5 mg/day) were all recommended to be given once daily. Gemigliptin is not on the list in China now, the recommended dose frequency and daily dose for Chinese patients with T2DM are still unknown. A dose of 50 mg/day gemigliptin is recommended for glycemic control in patients with diabetes in Korea. The results of the clinical trial from Rhee EJ et al. [16] found that the glycemic efficacy (including HbA1c, FPG, and P2hG) of twice daily was better than once daily. However, currently available data in this meta-analysis did not find a statistical difference in glycemic control when comparing sitagliptin with other three DPP-IV inhibitors directly.

Due to the similar glycemic efficacy, side effects can be considered for clinical choice as well. Even though, this meta-analysis showed that no statistical difference was found when comparing the total side effects and hypoglycemia. However other side effects including headache, back pain, infection and gastrointestinal side effects were not different as well. Moreover, there still existed the side effect of arthralgia when sitagliptin, saxagliptin and gemigliptin were used, and the incidence of arthralgia was higher in the group of sitagliptin than saxagliptin.

Although arthralgia is not a serious detrimental condition, it may impair the treatment adherence in patients with T2DM. Tarapués M et al. [24] reviewed the Spanish Pharmacovigilance System (SPvS) database from March 2007 to May 2012 and reported 332 suspected cases (208 for sitagliptin, 115 for vildagliptin, and nine for saxagliptin) might be associated with this side effect. Chaicha-Brom T et al. [25] also showed a case-report of DPP-IV inhibitors-associated arthralgias and found the direct association of DPP-IV inhibitors (sitagliptin and saxagliptin) and arthralgia's.

The arthralgia side effect of the DPP-IV inhibitors is poorly understood, and no exact mechanism has been reported. The potential mechanism could be explained by the increasing levels of P substance that is associated with pain, thus decreasing the pain threshold. The slightly increasing level of endomorphin-2 which related to pain sensitivity might be another reason [26]. Other studies found the reduction amount of CD26 (a glycoprotein related to the activity of DPP-IV enzyme) in arthritis and osteoarthritis [27, 28]. The results from Tarapués M et al. [24] also found the potential interaction of statins and DPP-IV inhibitors. Patients on both statins and DPP-IV inhibitors showed a shorter incubation period than patients with DPP-IV inhibitors monotherapy. This might be associated with the myalgia of statins and need further research. In conclusion, the modification of pain susceptibility, autoimmune disorder and the interaction between different drugs might be the potential mechanism. However, the reason the incidence of arthralgia was higher in patients treated with sitagliptin than saxagliptin is still unknown and needs further investigation.

In addition to the efficacy and safety of DPP-IV inhibitors, drug cost and cost-effective were also considered both for healthcare providers and patients. Teramachi H et al. [29] conducted a comparative survey of the cost of DPP-IV inhibitors (sitagliptin, vildagliptin, and alogliptin) and found that vildagliptin provides a superior cost-benefit by cost-effectiveness analysis. The recommended daily dose of different DPP-IV inhibitors was not the same, as well as the cost of these drugs. We searched the price of these agents on the Drug Centralized Procurement Network of Shandong Province (http://www.sdyypt.net/Website/). According to the recommended daily dose and suggested price, it was found that sitagliptin had the least daily cost while vildagliptin has the most costly. However, the largest difference of daily cost between these agents was less than 1.5 yuan, about 500 yuan per year. Nowadays, there are limited studies comparing both the hypoglycemic efficacy and cost-effectiveness of different DPP-IV inhibitors. More studies should be considered to conduct which might provide a guideline both for healthcare providers and patients.

This meta-analysis had its share of limitations. The methodological quality of each study in this meta-analysis was not good enough. Due to the limited number of RCTs, subgroup analysis for each comparison was not performed. Although all the enrolled patients were inadequately controlled patients with T2DM, the eligibility requirements of HbA1c, the additional treatment, except for DPP-IV inhibitors, and treatment duration were not the same. Furthermore, drug cost and cost-effective were not considered to compare. So, more head-to-head comparisons with larger sample sizes, higher quality, and strictly RCT design should be conducted in the future.

To summarize, it was concluded that sitagliptin was not superior to other three DPP-IV inhibitors, albeit all the four agents of DPP-IV inhibitors had good efficacy and safety. However, the risk of arthralgia should be given more attention when DPP-IV inhibitors were used in clinical settings. According to these findings, the treatment adherence and treatment cost may be considered first most by healthcare providers.

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Disclosure of conflict of interest

None.

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