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REVIEW ARTICLE

The efficacy and safety of dipeptidyl peptidase-4 inhibitors for type 2 diabetes: a Bayesian network meta-analysis of 58 randomized controlled trials

Juan Ling[1,2,3,4] · Peng Cheng[5] · Long Ge[1,2,3,4,6] · Ding-hua Zhang[7] · An-chen Shi[8] · Jin-hui Tian[1,2,3,4] · Ya-jing Chen[9] · Xiu-xia Li[1,2,3,4] · Jing-yun Zhang[1,2,3,4] · Ke-hu Yang[1,2,3,4]

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Abstract

Aims The aim is to evaluate the efficacy and safety of dipeptidyl peptidase-4 inhibitors (DPP4-I: sitagliptin, saxagliptin, linagliptin, vildagliptin and alogliptin) in patients with type 2 diabetes.

Methods We searched the Cochrane Library, PubMed, EMBASE, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), and the Wanfang Database from inception to April, 2018. Randomized controlled trials were included if they compared the different versions of DPP4-I with each other or with placebo in treatment of type 2 diabetes. Bayesian network meta-analysis and pairwise meta-analysis were performed to evaluate the efficacy and safety of the different kinds of DPP4-I and placebo. The data were analyzed using STATA 12.0 and WinBUGS1.4 software.

Results We identified 58 eligible studies (with 31356 patients) involving 14 treatment arms. Indirect comparison results showed that except for alogliptin, a decrease was found for all DPP4-I versus the placebo for hemoglobin A1c (HbA1c) with vildagliptin50 twice daily (BID) showing the highest probability. Linagliptin5 once daily (QD) decreased the level of fasting plasma glucose (FPG) the most for all DPP4-I versus the placebo; when comparing them with each other, alogliptin25QD was more effective when compared with sitagliptin100QD and vildaglipti50BID; linagliptin5qd had the highest decrease impact on body mass index (BMI). Except for hypoglycemia and upper respiratory tract infection (URTI), there are no statistical significance on incidence of adverse events and the body weight when DPP4-I are compared with each other or with placebo.

Conclusion Our network meta-analysis presents the associations of DPP4-I versus placebos on HbA1c, FPG, 2 h postprandial blood glucose (2HPPG), BMI, body weight and adverse events. DPP4-I have a lowering effect on the glycemic level (HbA1c, FPG), especially vildaglipti50BID and linagliptin10QD, respectively. Besides, linagliptin5QD has the greatest probabilities of reducing BMI. In addition, DPP4-I were associated with not increasing the incidence of adverse events. Among them, vildagliptin100QD and sitagliptin100QD have the lowest probability in reducing the incidence of hypoglycemia and URTI, respectively.

Keywords Dipeptidyl peptidase-4 inhibitors · Network meta-analyses · Type 2 diabetes mellitus

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Juan Ling and Peng Cheng are co-first authors.

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✉ Peng Cheng

✉ Ke-hu Yang
kehuyangebm2006@126.com

Extended author information available on the last page of the article

Introduction

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Type 2 diabetes used to be called non-insulin-dependent diabetes or adult-onset diabetes, accounting for at least 90% of all cases of diabetes. According to the International Diabetes Federation (IDF), over 350 million adults are currently at high risk of developing type 2 diabetes, the most prevalent form of the disease. There is a projected rise in the numbers to 700 million people living with diabetes in the world by the year 2045 [1]. In China, increasing affluence and lifestyle

changes have led to dramatic increases in the prevalence of T2DM as out of the 1.9 million deaths among adults in China in 2015, 1.3 million dead due to diabetes with 40.8% of these deaths occurring in people under 60 [2]. This means that more and more people will need to be prescribed antidiabetic medication to help achieve the recommended target levels of HbA1c, FPG, 2HPPG, BMI, body weight, and so on.

An increasing number of patients with type 2 diabetes mellitus (T2DM) are being treated with dipeptidyl peptidase-4 inhibitors (DPP4-I), a new therapeutic class of oral anti-hyperglycemic drugs for T2DM. These agents have been shown to reduce HbA1c levels without increasing the risk of hypoglycemia and weight gain [3]. The use of DPP4-I as a T2DM therapy [4] has now been firmly established with numerous inhibitors in varying stages of clinical development. Four DPP4-I (sitagliptin [5], saxagliptin [6], linagliptin [7], and alogliptin [8]) have already been approved for this indication by the US Food and Drug Administration.

Most meta-analyses were published focusing on the efficacy and safety of different DPP4-I for type 2 diabetes as compared to placebo [9–11]. However, there were many limitations for these studies, such as which therapy among DPP4-I have the highest probability in different outcomes. Obviously, it was difficult for randomized controlled trials (RCTs) and pairwise meta-analysis to integrate information on the relative efficacy of all available DPP4-I. Network meta-analysis has become increasingly popular for evaluating interventions, which can estimate the relative effectiveness of all interventions and give rank ordering of the interventions even if some head-to-head comparisons are lacking [12]. Therefore, we systematically conducted a Bayesian network meta-analysis to rank and compare the outcomes of different DPP4-I agents for treating T2DM.

Methods

Data sources and search strategy

We searched the following databases for a time period ranging from their inception to April 2018 for randomized controlled trials: The Cochrane Library, PubMed, EMBASE, CBM, CNKI, and the Wanfang Database. We limited our search to human subjects only and the search strategy was developed by LG and KHY, who have more than 10 years of experience as information specialists. We combined both MeSH and free text terms for identifying the relevant articles, for the Medline search we used a highly sensitive filter for identifying randomized trials which are developed by the Cochrane Collaboration [13]. The search terms used were as following: DPP4 Inhibitor, sitagliptin, linagliptin, saxagliptin, vildagliptin, alogliptin, NIDDM, random*, randomized controlled trial*, randomized trial*. The search strategy was developed by two authors. No language restriction was applied. Search strategies used for each English electronic database are listed in Supplementary material A1 and were adapted using the appropriate Chinese terms for Chinese electronic databases. We did not consider any ongoing studies.

Eligibility criteria

Studies that met the following criteria were included: (1) type of studies—RCTs, we excluded non-randomized clinical trials; (2) types of participants—patients with T2DM regardless of age, gender, or ethnic origins; (3) interventions—DPP4-I for the treatment of T2DM, including sitagliptin, linagliptin, saxagliptin, vildagliptin, and alogliptin; (4) comparators—different types of DPP4-I as noted above or placebo agents; (5) outcomes—the primary outcomes are HbA1c and FPG, the second outcomes are BMI, 2HPPG, body weight and adverse events, including hypoglycemia, diarrhea, URTI, hypersensitivity reaction (HR), renal and hepatic toxicity. This article is based on previously conducted studies and does not contain any studies on animals performed by any of the authors.

Study selection

The two authors reviewed the article titles and abstracts independently to select studies that met the inclusion criteria. Another author was consulted whenever there was any disagreement regarding the study selection. The study selection process is presented in a flowchart based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [14] (Supplementary material A1).

Data extraction and assessment of risk of bias

The study data were independently extracted by the two authors using a data collection form with Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, USA). The items extracted contained study information (author, year of publication, sample size, trial duration, study arms, and outcomes) and patient characteristics (median age, background therapy, diabetes duration, length of follow-up, baseline level of HbA1c, BMI, and FPG). Any discrepancies that appeared were resolved with the consensus from the two independent reviewers or by a senior investigator. The original investigators were contacted by email whenever we had questions regarding their articles.

Geometry of the network

Network plots were drawn to describe and present the geometry of different treatments using STATA 12.0 software. Trials were excluded if they were not connected by treatments. The network is represented in a ring-shaped graph, nodes were used to represent different interventions, edges to represent the head-to-head comparisons between interventions and the density thickness of the lines show the trial amount [15].

Risk of bias in individual studies

The quality of the studies was assessed using a risk of quality assessment tool recommended by the Cochrane Handbook version 5.1.0 [13], including method of random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete information, selective reporting, and other biases. The methodological quality were all classified into low, high, or unclear risk of bias based on the guidelines from the Cochrane Collaboration [16]. The risk of bias assessment was completed by two independent reviewers and any conflicts in the assessment of this data were resolved through discussion until consensus was reached.

Data synthesis and analysis

Methods for direct treatment comparisons

We performed pairwise meta-analysis using STATA 12.0 software (Stata Corporation, College Station, TX, USA) with the DerSimonian–Laird random-effects model [17, 18]. To measure the effects, WMD (weighted mean differences) were calculated for changes in HbA1c, BMI, 2HPPG, body weight and FPG with 95% CI (confidence interval), RR (risk ratio) for adverse events, including hypoglycemia, diarrhea, URTI, hypersensitivity reaction (HR), renal and hepatic toxicity with 95% CI were calculated. Statistical heterogeneity [19, 20] was assessed by X^2 statistics and I^2 statistic. When the P value was ≥ 0.1, and I^2 was $\leq 50\%$, it suggested that there was no statistical heterogeneity and the Mantel–Haenszel random-effects model was used for performing meta-analysis [13]. When the P value was < 0.1, and I^2 was $> 50\%$, we explored sources of heterogeneity by subgroup analysis [21] and meta-regression [22].

Methods for indirect and mixed comparisons

A new Bayesian network meta-analysis was conducted using WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) [23, 24]. The random-effects model with vague priors for multi-arm trials was applied (Supplementary material A2). Model parameters were estimated using a Markov chain Monte Carlo (MCMC) method called Gibbs sampling. We first generated 50,000 simulations for each chain, and these simulations then were discarded as the "burn-in" period. Then posterior summaries were based on 100,000 subsequent simulations. The different chains were as follows: (1) chain 1: treatment effect: $[d\,(k) = 0]$; sd = 1; mu $(i) = 0$; (2) chain 2: treatment effect: $[d\,(k) = -1]$; sd = 2; mu $(i) = -3$; (3) chain 3: treatment effect: $[d\,(k) = 2)$; sd = 4; mu (i) = random between -7 and $+7$ (based on Excel-2013 generated random numbers); where $d\,(k)$ = treatment effect of experimental intervention "k" compared with reference and mu (i) = treatment effect of the experimental intervention compared with control in the trial "i". The model convergence was assessed by trace plots and Brooks–Gelman–Rubin plots [25].

To rank the treatments based on efficacy and safety, we calculated the probabilities of the surface under the cumulative ranking curve (SUCRA), SUCRA can illustrate the outcome percentages of every treatment relative to an ideal treatment. SUCRA value is 100% for the best treatment and 0% for the worst treatment, a higher SUCRA value relates to a higher probability for the drug to rank high [26]. In this study, for all DPP4I agents outcomes a higher number is consistent with a reduction in T2DM occurrence. For the adverse event outcome, the agent associated with the higher risk of serious adverse events received a higher score.

Inconsistency refers to differences between direct and various indirect effect estimates for the same comparison [27]. If a loop connecting three arms existed, network inconsistency was evaluated by comparing the direct estimates with the indirect estimates for each comparison, we estimated the inconsistency factors (IF, the difference between the direct and indirect estimate for one of the comparisons in a particular loop) in closed loop with a loop-specific approach described by Chaimani et al. [15]. We identified inconsistency as yielding a lower 95% CI limit that does not reach 1.

To formally check whether a model's overall fit was satisfactory, an absolute measure of fit $\bar{D}$res, was considered to formally check the model's overall fit. $\bar{D}$res is the posterior mean of the residual deviance (the deviance for the fitted model minus the deviance for the saturated model) used to ensure the general fit of the model. Ideally, each data point should contribute about one to the posterior mean deviance so that it can be compared to the number of data points for the purpose of checking model fit. To ascertain the model's fit, the number of data points is compared to the posterior mean deviance, which is contributed with approximately one from each data point [28].

We searched the Chinese language databases to include the studies. Although one study indicated that the quality of reporting and methodology is the similar in China and other countries [29], we conducted the subgroup analysis

using STATA 12.0 software and WinBUGS 1.4.3 software. In addition, random-effects meta-regression analyses [22] were performed to handle the issue of imbalance between studies among baseline characteristics (Table 1) by performing RStudio (ver. 0.96.315; RStudio Inc, Boston, MA, USA) and we described the details of software commands in Supplementary material A2. We conducted the meta-regression analyses of mean age and disease duration in the baseline information for primary outcomes including HbA1c and FPG.

Results

Study selection

A total of 13,697 records were identified from the electronic databases with 19 references identified from other sources. After screening them by title and abstract, we retrieved 283 articles for further assessment. Finally, 58 RCTs [30–87] involving 31,356 patients were included. The search results and selection details are shown in Fig. 1.

Study characteristics and quality assessment

Table 1 summarizes the characteristics of the included 58 trials that qualified for this network meta-analysis. The studies were published between 2008 and 2017. During this period of time, a total of 31,356 participants were enrolled in the original studies and in this pooled analysis. The trial duration ranged from 4 to 54 weeks. The average age of the included patients was 58.8 years [standard deviation (SD), 7.31] and varied from 33.1 to 74.9 years. The median diabetes duration at baseline was 7.4 years [interquartile range (IQR), 13.4–33.1] years while the mean baseline HbA1c, FPG, BMI levels were at 8.07% (SD 0.61%), 9.00 mmol/L (SD 1.04 mmol/L), 27.87 kg/m^2 (SD 3.74 kg/m^2), respectively. Among the 59 studies, which were mostly multiple-arm trials, patients were treated with vildagliptin in 22 studies, sitagliptin100QD in 24 studies, saxagliptin in 13 studies, linagliptin in 13 studies, and alogliptin in 5 studies.

The results of assessment of risk of bias showed that 71.2% of studies were judged to have a low risk of bias in terms of blinding of patients and personnel, 69.5% for concealment of allocation and blinding of outcome assessors, 24 RCTs (40.7%) mentioned the methods of adequate sequence generation. Forty-two RCTs were double-blind design, six RCTs were open-label design (Supplementary material A3).

Evidence network

The network plots are presented in Fig. 2a–j. Fifteen treatments were analyzed, including five in the DPP4-I dose-group (sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin) and placebo. In total, 82.8% (48/58) of the trials were two-arm studies and the rest (18.64%) were multiple-arm studies (see Table 1; Fig. 2). Overall, the analysis of HbA1c (Fig. 2a, including 48 studies, 12 treatments), FPG (Fig. 2b, including 40 studies, 12 treatments), 2HPPG (Fig. 2c, 19 studies, 6 treatments), BMI (Fig. 2d, 10 studies, 6 treatments), body weight (Fig. 2e, 5 studies, 5 treatments), hypoglycemia (Fig. 2f, 26 studies, 11 treatments), diarrhea (Fig. 2g, 12 studies, 6 treatments), URTI (Fig. 2h, 9 studies, 9 treatments), HR (Fig. 2i, 4 studies, 7 treatments), renal and hepatic toxicity (Fig. 2j, 4 studies, 5 treatments) were presented, respectively. Every group of DPP4-I had existing head-to-head (direct) comparisons with placebo.

Traditional pairwise meta-analysis of individual DPP4-I with dose distinction

Supplementary material A4 summarizes the results of pairwise meta-analysis regarding the outcomes. There was no significant statistical heterogeneity in the pooled analysis of all of the included studies ($I^2 < 50.0\%$, $P > 0.1$). Regarding HbA1c, except vildagliptin50QD, vildagliptin100QD, linagliptin5QD, saxagliptin2.5QD, linagliptin10QD, vildagliptin50BID, saxagliptin5QD, linagliptin0.5QD, alogliptin25QD and sitagliptin100QD significantly reduced the level of HbA1c in comparison to the placebo. Besides, vildagliptin50BID were more effective in reducing the level of HbA1c when compared with sitagliptin100QD by 0.49 (95% CI 0.47, 0.51). No statistically significant difference was found between DPP4-I in their effects on HbA1c. WMD with 95% CIs are listed in Supplementary material A4.

For FPG control, vildagliptin100QD, linagliptin5QD, linagliptin10QD, sitagliptin100QD, alogliptin25QD, alogliptin12.5QD, saxagliptin5QD and sitagliptin50QD significantly resulted in a significant decline in FPG when compared to the placebo. Besides, vildagliptin50QD reduced the BMI in comparison to the placebo by − 1.25 (95% CI − 1.53, − 0.98). As for body weight, vildagliptin100QD were associated with an increase in body weight when compared to the placebo and alogliptin25QD reduced the body weight in comparison to the placebo by − 0.32 (95% CI − 1.39, − 0.25). For 2HPPG control, statistically significant reduction was detected for linagliptin5QD was associated with a decreased 2HPPG as compared with vildagliptin50BID by − 0.84 (95% CI − 1.32, − 0.36).

As for adverse events, linagliptin10QD increased the incidence of renal and hepatic toxicity in comparison to the placebo by 0.75 (95% CI 1.12, 4.61). No statistically significant difference in occurrences of diarrhea, hypoglycemia, URTI and HR between any comparisons was detected.

Table 1 Characteristics of the 58 studies included in the network meta-analysis

Study ID	Treatments	No. of study sites	Study phase	Size (pts)	Length of follow-up (weeks)	Background therapy	Duration of trial (weeks)	Baseline information				
								Mean age (years)	Disease duration	Mean HbA1c (%)	Mean BMI[b] (kg/m^2)	Mean FPG[c] (mmol/L)
Xiaoyan (2016) [30]	Vildagliptin50BID, saxagliptin5qd	–	–	73	–	Met + SU	24	62.9	7	8.4	23.5	8.2
Koyanagawa (2016) [31]	Vildagliptin50BID, sitagliptin100qd	–	–	33	–	Insulin	8	65.2	16.6	7.2	–	–
Asti (2016) [32]	Sitagliptin100QD, saxagliptin100qd	–	–	128	16	Met	–	64.3	6.5	–	–	–
Huang (2015) [33]	Vildagliptin50BID, saxagliptin5qd	–	–	64	–	Insulin	12	48.5	7.61	8.6	24.48	9.3
Chen (2015) [34]	Placebo, sitagliptin100qd, linagliptin5qd	–	–	90	–	Met 500TID	12	–	–	8.2	25.3	9.8
Tang (2015) [35]	Vildagliptin50BID, sitagliptin100qd, linagliptin5qd	–	–	535	12	Insulin + Met	12	55.6	7.93	9.5	26.6	9.9
Kothny (2015) [36]	Vildagliptin50QD, sitagliptin25qd	87	–	148	–	–	24	66.8	19.1	7.6	33.19	7.9
Göke (2014) [37]	Vildagliptin50BID, sitagliptin50bid	–	–	196	–	Met	2	61.2	6.3	–	–	7.8
Li (2014) [38]	Sitagliptin100QD, saxagliptin5qd	–	–	50	–	–	12	33.1	7.1	8.6	23.2	10.9
Takihata (2014) [39]	Sitagliptin50QD, vildagliptin100qd, alogliptin25qd	–	–	305	24	Met + SU	24	–	–	7.1	–	–
Li (2014) [40]	Saxagliptin5QD, vildagliptin50bid, sitagliptin100qd	–	–	190	–	Met + Glim/Aca/Piog	24	46.6	5	8.7	26.3	8.5
Sakamoto (2012) [41]	Vildagliptin50BID, sitagliptin50qd	–	–	20	–	–	4.5	55.2	4.5	7.9	25.1	–
Rizzo (2012) [42]	Sitagliptin100QD, vildagliptin50bid	–	–	90	–	–	12	60	8.6	8.4	29.5	8.2
Guerci (2012) [43]	Vildagliptin50BID, placebo	7	–	38	–	Met	8	56.3	6.9	7.1	31.7	–
Wang (2016) [44]	Linagliptin5QD, placebo	–	–	306	–	–	24	47.1	–	8	21.7	8.8
Yang (2015) [45]	Vildagliptin50QD, placebo	–	–	279	–	Glim	24	58.5	6.9	8.7	24.9	10.3

Table 1 (continued)

Study ID	Treatments	No. of study sites	Study phase	Size (pts)	Length of follow-up (weeks)	Background therapy	Duration of trial (weeks)	Baseline information				
								Mean age (years)	Disease duration	Mean HbA1c (%)	Mean BMI[b] (kg/m^2)	Mean FPG[c] (mmol/L)
Sheu (2015) [46]	Linagliptin5QD, placebo	–	III	154	–	Insulin	24	51.1	5	8.6	25.9	7.4
Schmieder (2015) [47]	Linagliptin10QD, placebo	–	–	62	–	–	6	57	–	7	–	7.6
Mathieu (2015) [48]	Sitagliptin100QD, placebo	–	–	660	–	–	24	58.8	13.5	8.6	32.1	9.8
Leibowitz (2015) [49]	Saxagliptin5QD, placebo	788	–	16,492	–	CAM	96	65	12	8	31.2	8.7
Laakso (2015) [50]	Linagliptin5QD, placebo, glim	–	–	235	40	Insulin	52	66.6	–	8.1	–	–
Kaku (2015) [51]	Sitagliptin25QD, sitagliptin50qd, placebo	–	–	242	–	–	8	63.3	–	6	25.3	5.9
Wu (2013) [52]	Saxagliptin5QD, placebo	–	–	21	–	–	24	50.5		8.3	25.1	9.1
Yang (2012) [53]	Sitagliptin100QD, placebo	17	–	395	–	Met	24	54.6	6.9	8.5	25.3	9.6
Rauch (2012) [54]	Linagliptin5QD, placebo	–	–	80	2	–	4	–	–	7.3	40	9.3
Pan (2012) [55]	Saxagliptin5QD, placebo	40	III	568	–	–	24	51.4	1	8.2	25.9	9.1
Pan (2012) [56]	Vildagliptin50BID, vildagliptin50qd, placebo	–	–	438	–	Met	24	54.1	5.03	8	25.5	8.8
Minervini (2012) [57]	Saxagliptin5QD, placebo	–	III	455	–	Insulin	24	–	10	8.7	–	9.6
Kothny (2012) [58]	Vildagliptin50QD, placebo	–	–	525	–	Insulin + OADs	52	66.5	16.7	7.8	30.3	8.7
Kawamori (2012) [59]	Linagliptin5QD, linagliptin10qd, placebo	47	IIb/III	561	–	–	12	60	5	8	25	9.1
Derosa (2012) [60]	Vildagliptin50BID, placebo	–	–	171	–	Met	48	53.7	25.2	8.7	28	8.01
Derosa (2012) [61]	Sitagliptin100QD, placebo	–	–	178	–	Met	48	55.3	5.6	8.1	28.5	7.9
Barnett (2012) [62]	Linagliptin5QD, placebo	–	III	241	–	Met + SU/insulin	24	74.9	–	7.8	30.7	–

Table 1 (continued)

Study ID	Treatments	No. of study sites	Study phase	Size (pts)	Length of follow-up (weeks)	Background therapy	Duration of trial (weeks)	Baseline information				
								Mean age (years)	Disease duration	Mean HbA1c (%)	Mean BMI[b] (kg/m^2)	Mean FPG[c] (mmol/L)
Tajima (2011) [63]	Sitagliptin50QD, placebo	34	–	138	–	Glim	12	60.8	9.1	8.4	24.6	8.6
Seino (2011) [64]	Alogliptin6.25OD, alogliptin12.5OD, alogliptin25od, alogliptin50od, placebo	54	II	480	–	–	12	58.9	6.5	7.9	24.7	–
Prato (2011) [65]	Linagliptin5QD, placebo	–	III	503	–	one OAD	24	55.7	–	8	29.05	9.1
Nowicki (2011) [66]	Saxagliptin2.5QD, placebo	–	–	170	–	OADs + insulin	12	67	16.7	8.3	30.7	9.7
Nowicki (2011) [67]	Saxagliptin2.5QD, placebo	–	–	164	–	Insulin	5	67	–	8.2	–	10.1
Newman (2011) [68]	Linagliptin5QD, placebo	53	–	133	–	–	12	64	5	8.2	–	–
Lukashevich (2011) [69]	Vildagliptin50QD, placebo	–	–	525	–	CAM	24	66.7	16.4	7.8	30	8.6
Lukashevich (2011) [70]	Vildagliptin50QD, placebo	–	–	221	–	insulin + OADs	24	64	19	8.7	–	–
Kothny (2011) [71]	Vildagliptin50QD, placebo	–	–	221	–	OAD/insulin	24	64.3	18.1	7.7	30	–
Janet (2011) [72]	Linagliptin5QD, placebo	53	–	133	1	GLDs	52	64.4	5	8.2	32	8.6
Horie (2011) [73]	Linagliptin0.5QD, linagliptin2.5QD, linagliptin10qd, placebo	5	–	72	–	–	4	60	–	6.8	24.6	8
Dandona (2011) [74]	Sitagliptin100QD, placebo	–	–	22	–	–	12	55	–	7.7	34.9	–
Barzilai (2011) [75]	Sitagliptin100QD, placebo	52	–	206	–	–	24	72	7.1	7.8	31	9.6
Garber (2008) [76]	Vildagliptin50QD, placebo, vildagliptin100qd	114	–	515	–	Glim 4QD	24	58.2	7.2	8.5	31.3	10.4
DeFronzo (2008) [77]	Alogliptin12.5QD, alogliptin25qd, placebo	–	–	329	–	–	26	53.4	–	7.9	–	11.3

Table 1 (continued)

Study ID	Treatments	No. of study sites	Study phase	Size (pts)	Length of follow-up (weeks)	Background therapy	Duration of trial (weeks)	Baseline information				
								Mean age (years)	Disease duration	Mean HbA1c (%)	Mean BMI[b] (kg/m^2)	Mean FPG[c] (mmol/L)
Chan (2008) [78]	Sitagliptin50QD, placebo	–	–	91	–	Glip5QD	54	67.9	13.5	7.7	26.6	8.8
Su (2014) [79]	Vildagliptin100QD, placebo	–	–	294	–	Aca	12	–	–	8.82	24.39	9.14
Lukashevich (2012) [80]	Vildagliptin50BID, placebo	–	–	169	–	–	24	59	13	8.82	–	–
Moses (2012) [81]	Saxagliptin5QD, placebo	–	IIIb	257	–	Met+SU	24	57		8.28	29.3	–
Su (2014)[a] [82]	Vildagliptin100QD, placebo	–	–	311	–	Met	12	47.99	27.59	8.69	–	9.06
Ba (2016) [83]	Sitagliptin100QD, placebo	32	III	440	–	Met+Glim+Glic	24	57	7	8.55	25.35	10.7
Pan (2017) [84]	Alogliptin25QD, placebo	3	III	586	–	–	4	52.4	2	8	25.9	–
Shah (2017) [85]	Sitagliptin100QD, placebo	–	–	32	4–5	–	4	56.3	12.9	7.21	34.4	–
Tanaka (2017) [86]	Alogliptin25QD, vildagliptin50bid	–	–	48	–	–	24	64.7	8.9	7.3	24.9	7.8
Wang (2017) [87]	Sitagliptin100QD, placebo	5	–	818	–	Aca	34	57.2	7.8	8.1	26	9.8

Met metformin, *SU* sulfonylurea, *OADs* oral anti-diabetic drugs, *Glim* glimepiride, *Piog* pioglitazone, *GLP* glipizide, *Glic* gliclazide, *CAM* current anti-diabetic medication, *GLDs* glucose-lowering drugs, *Aca* acarbose

–, unavailable information; [a]the sample size of HbA1c ($n=29,848$); [b]the sample size of BMI ($n=1541$); [c]the sample size of FPG ($n=27,858$)

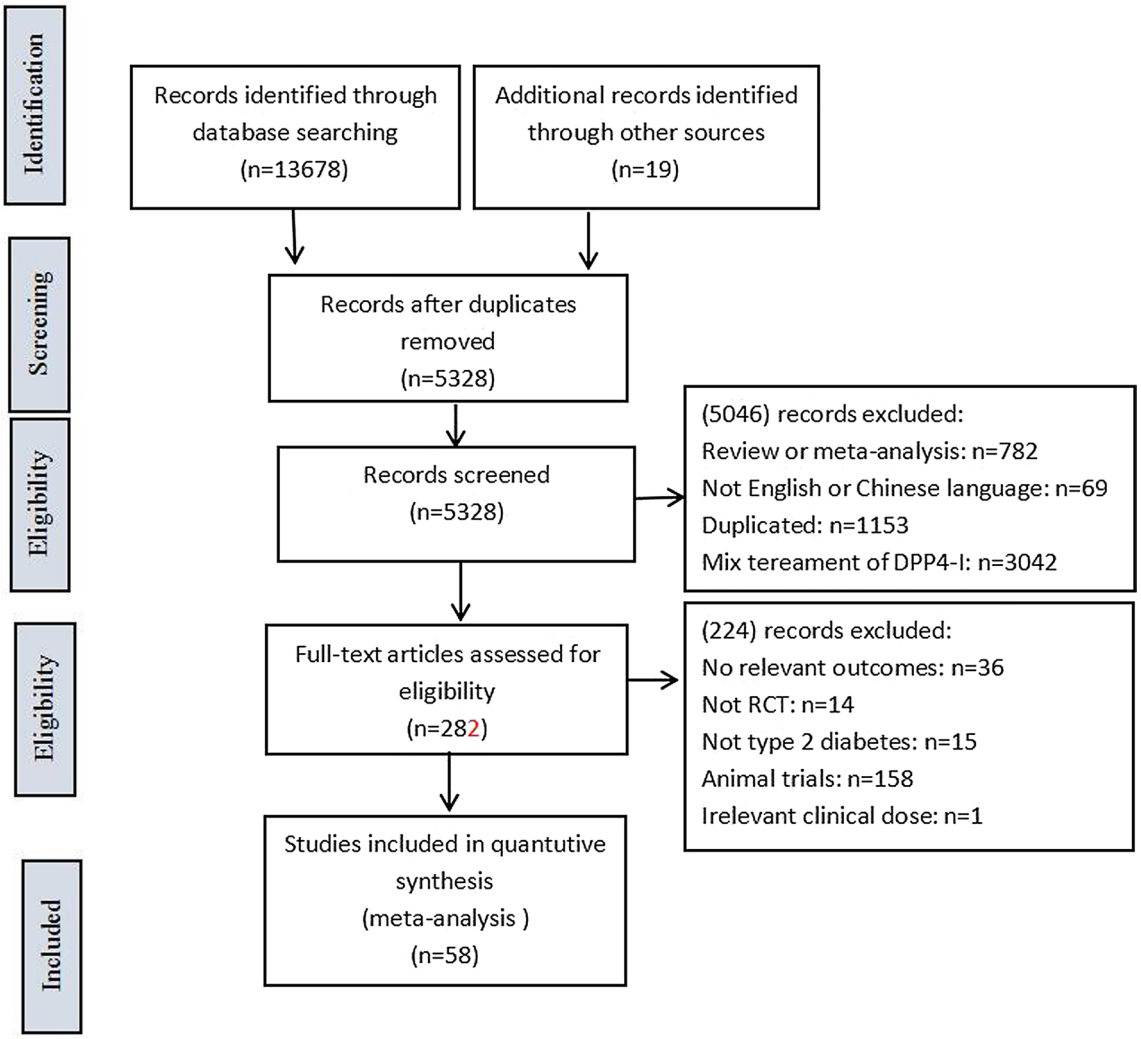


Fig. 1 The flow chart of the trials selection

Network meta-analysis of individual DPP4-I with dose distinction

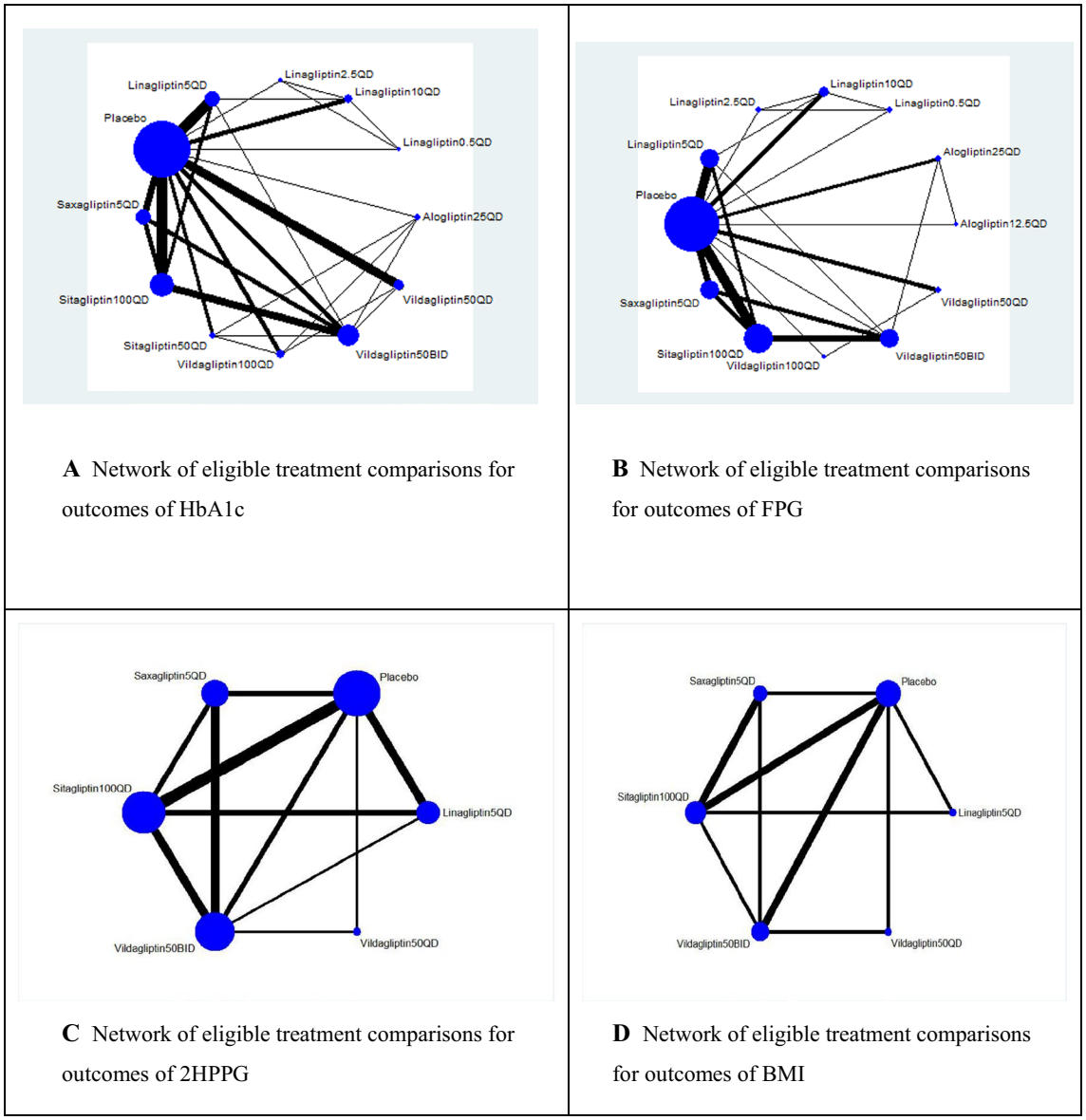
The results of the network meta-analysis of the DPP4-I, placebo, and other comparators are displayed in Table 2. Vildagliptin50BID, linagliptin10QD saxagliptin5QD, and sitagliptin50QD were associated with a decline in HbA1c versus the placebo with − 1.26 (95% CI − 2.29, − 0.22), − 1.01 (95% CI − 1.66, − 0.46), − 0.57 (95% CI − 0.37, − 1.51) and − 0.67 (95% CI − 1.34, − 0.02). In addition, sitagliptin100QD, vildagliptin50QD, linagliptin5QD were relevant with reducing the level of HbA1c by 0.69 (95% CI 0.07, 1.32), 0.93 (95% CI 0.03, 1.82) and 0.83 (95% CI 0.01, 1.64), respectively, when compared with vildagliptin50BID.

As for FPG, linagliptin5QD and alogliptin25QD were better than the placebo in reducing the level of FPG with − 1.74 (95% CI − 2.89, − 0.58) and − 0.91 (95% CI − 1.62, − 0.21), respectively. Moreover, sitagliptin50QD resulted in significantly lower incidences of hypoglycemia compared with vildagliptin100QD by 6.02 (95% CI 1.09, 33.66). Linagliptin5QD was associated with a 13.90 reduction in BMI when compared with the placebo and it also had a greater decrease in BMI when compared to other drugs of DPP4-I.

As for adverse events, vildagliptin100QD was inferior to sitagliptin50QD in reducing the incidence of hypoglycemia, and sitagliptin100QD was inferior to the placebo in reducing the incidence of URTI with 0.72 (95% CI 1.15, 2.93). No other significant reductions in incidence of diarrhea, 2HPPG, renal and hepatic toxicity, body weight and hypersensitivity reaction between any comparisons were detected.

Ranking of different doses of DPP4-I on outcomes

Table 3 presents the mean values of SUCRA, providing the hierarchy of 16 treatments on outcomes. According to SUCRA, vildaglipti50BID and linagliptin10QD have



A Network of eligible treatment comparisons for outcomes of HbA1c

B Network of eligible treatment comparisons for outcomes of FPG

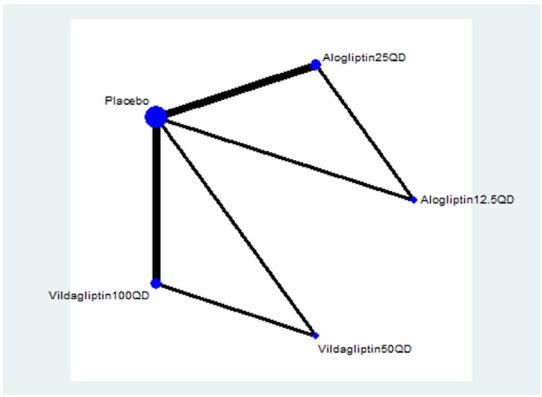
C Network of eligible treatment comparisons for outcomes of 2HPPG

D Network of eligible treatment comparisons for outcomes of BMI

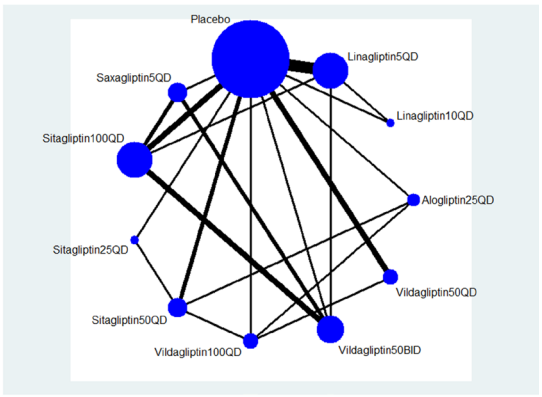
Fig. 2 Network of eligible treatment comparisons for outcomes of HbA1c (**a**), FPG (**b**), 2HPPG (**c**), BMI (**d**), body weight (**e**), hypoglycemia (**f**), diarrhea (**g**), upper respiratory tract infection (**h**), renal and hepatic toxicity (**i**) and hypersensitivity reaction (**j**). Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size)

the higher probability in reduction effect on HbA1c with probabilities of 0.8374 and 0.8071, respectively. Regarding the effect on FPG, linagliptin5QD and alogliptin25QD decreased FPG most with probabilities of 0.9338 and 0.7434. With respect to 2HPPG, saxagliptin5QD and sitagliptin100QD decreased 2HPPG most with probabilities of 0.746 and 0.6881. Vildagliptin50QD and sitagliptin100QD decreased BMI most with probabilities of 0.8379 and 0.6596, respectively. In terms of body weight, vildagliptin100QD and placebo reduced the body weight most with probabilities of 0.6571 and 0.7954.

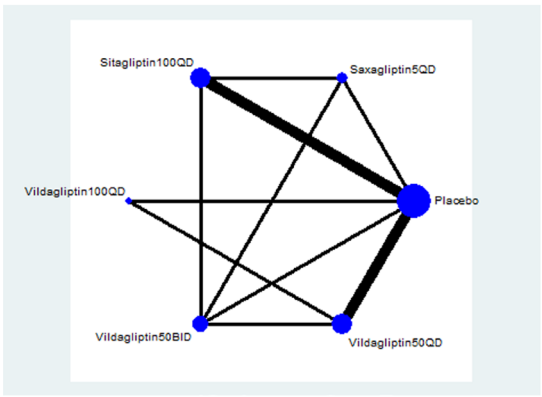
For adverse events, the most harmful treatments for hypoglycemia were vildagliptin100QD (0.8836) and linagliptin5QD (0.7431). In addition, the most harmful treatments for diarrhea, renal and hepatic toxicity, URTI and HR were vildagliptin100QD (0.5583), linagliptin5QD (0.6616), sitagliptin100QD (0.7567) and linagliptin5QD (0.6603), respectively.



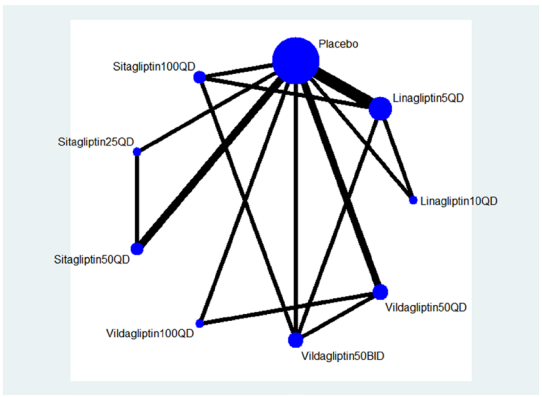
E Network of eligible treatment comparisons for outcomes of body weight



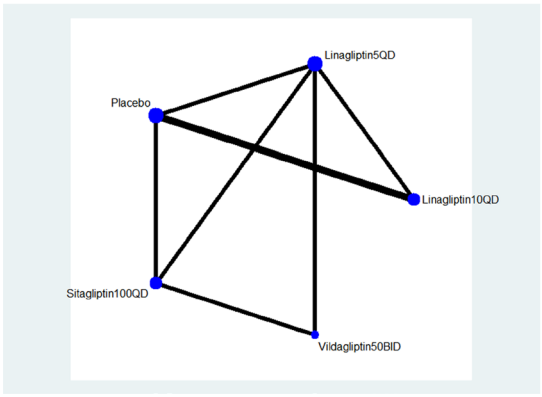
F Network of eligible treatment comparisons for outcomes of hypoglycaemia



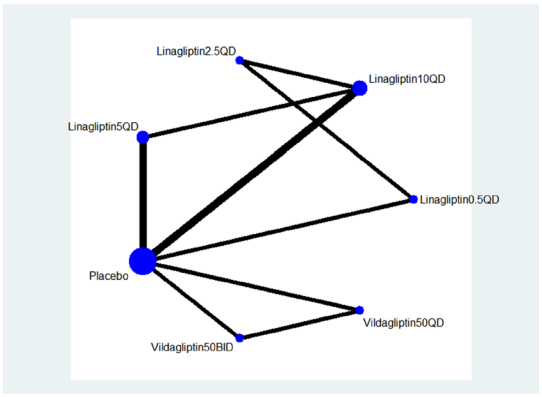
G Network of eligible treatment comparisons for outcomes of diarrhea



H Network of eligible treatment comparisons for outcomes of upper respiratory tract infection



I Network of eligible treatment comparisons for outcomes of renal and hepatic toxicity



J Network of eligible treatment comparisons for outcomes of hypersensitivity reaction

Fig. 2 (continued)

Table 2 Network meta-analysis of individual DPP4-I for with dose distinction

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Placebo (reference)										
Vildagliptin50BID	**−1.26 (−2.29, −0.22)**	0.19 (−0.37, 0.77)	0.63 (−0.10, 1.35)	0.10 (−0.68, 0.88)	0.64 (−1.09, 2.38)	1.05 (0.47, 2.15)	1.09 (0.27, 3.93)	1.04 (0.22, 4.56)	1.7 (0.03, 15.1)	4.94 (0.03, 12.58)
Sitagliptin100QD	0.37 (−0.17, 0.91)	0.47 (−0.03, 0.98)	0.40 (−0.32, 1.12)	0.06 (−0.54, 0.65)	–	1.19 (0.66, 2.11)	1.37 (0.46, 3.89)	**0.72 (2.93, 1.15)**	1.06 (0.05, 28.36)	–
Vildagliptin50QD	0.13 (−0.59, 0.84)	0.19 (−0.93, 1.31)	0.32 (−0.84, 1.49)	0.03 (−1.07, 1.14)	0.04 (−1.23, 1.29)	1.47 (0.70, 3.08)	0.98 (0.37, 2.57)	1.79 (0.32, 7.39)	–	1.18 (0.02, 354.4)
Sitagliptin50QD	**−0.57 (−0.37, −1.51)**	–	–	–	–	0.55 (0.18, 1.70)	–	0.76 (0.13, 3.62)	–	–
Saxagliptin5QD	**−0.67 (−1.34, −0.02)**	0.53 (−0.07, 1.16)	0.31 (−0.53, 1.14)	0.23 (−0.50, 1.00)	–	2.12 (0.86, 5.51)	1.54 (0.42, 6.22)	–	–	–
Linagliptin5QD	0.24 (−0.39, 0.86)	0.44 (−0.19, 1.07)	**−13.90 (−15.11, −12.72)**	**−1.74 (−2.89, −0.58)**	–	0.90 (0.54, 1.38)	–	1.19 (0.41, 3.00)	0.74 (0.05, 10.27)	2.41 (0.53, 92.28)
Linagliptin10QD	**−1.01 (−1.66, −0.46)**	–	–	0.75 (−0.34, 1.85)	–	1.21 (0.18, 8.68)	–	1.16 (0.23, 5.94)	1.03 (0.02, 49.60)	1.40 (0.02, 41.33)
Vildaglipt-in100QD	0.59 (−0.29, 1.48)	–	–	0.16 (−1.58, 1.92)	−0.24 (−1.19, 0.71)	3.32 (0.84, 13.37)	0.59 (0.11, 2.94)	1.96 (0.29, 12.57)	–	–
Linagliptin0.5QD	0.92 (−0.76, 2.61)	–	–	0.19 (−1.58, 1.97)	–	–	–	–	–	0.42 (0.00, 111.2)
Alogliptin25QD	0.52 (−0.56, 1.59)	–	–	**−0.91 (−1.62, −0.21)**	0.69 (−0.27, 1.66)	2.74 (0.59, 14.49)	–	–	–	–
Sitagliptin25QD	–	–	–	–	–	1.20 (0.30, 5.00)	–	2.45 (0.32, 21.4)	–	–
Linagliptin2.5QD	0.63 (−1.13, 2.39)	–	–	0.32 (−1.49, 2.15)	–	1.20 (0.30, 5.00)	–	–	–	0.53 (0.00, 125.4)
Alogliptin12.5QD	–	–	–	1.05 (−0.70, 2.82)	0.38 (−0.92, 1.66)	–	–	–	–	–
Vildagliptin50BID (reference)										
Sitagliptin100QD	**0.69 (0.07, 1.32)**	0.28 (−0.29, 0.84)	–	−0.05 (−0.08, 0.71)	–	1.13 (0.55, 2.57)	1.27 (0.28, 6.16)	0.69 (0.13, 3.40)	0.63 (0.01, 28.51)	–
Vildagliptin50QD	**0.93 (0.03, 1.82)**	0.00 (−1.13, 1.11)	−0.30 (−1.48, 0.86)	−0.07 (−1.43, 1.28)	–	1.40 (0.50, 4.24)	0.90 (0.22, 4.04)	1.72 (0.21, 10.30)	–	0.24 (0.00, 42.28)
Sitagliptin50QD	−0.49 (−1.51, 0.55)	–	–	–	–	0.53 (0.14, 2.11)	–	0.72 (0.07, 6.42)	–	–
Saxagliptin5QD	−0.39 (−1.11, 0.33)	0.34 (−0.25, 0.95)	−0.32 (−1.18, 0.64)	0.13 (−0.69, 0.95)	–	2.01 (0.76, 6.19)	1.44 (0.29, 8.24)	–	–	–

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Linagliptin5QD	**0.83 (0.01, 1.64)**	0.25 (−0.49, 0.99)	**−14.53 (−15.86, −13.20)**	0.81 (−0.16, 1.77)	–	0.85 (0.40, 1.95)	–	1.15 (0.25, 4.81)	0.44 (0.01, 19.64)	0.48 (0.00, 271.8)
Linagliptin10QD	0.19 (−0.10, 1.39)	–	–	0.66 (−0.68, 1.98)		1.16 (0.16, 9.23)	–	1.12 (0.15, 9.10)	0.61 (0.00, 0.61)	0.28 (0.00, 122.2)
Vildaglipt-in100QD	−0.47 (−1.50, 0.56)	–	–	0.06 (−1.86, 1.97)	–	3.15 (0.69, 16.32)	0.54 (0.07, 4.37)	1.88 (0.19, 18.19)		
Linagliptin0.5QD	−0.14 (−1.91, 1.66)	–	–	0.09 (−1.83, 2.02)	–	–	–			0.074 (0.00, 164.9)
Alogliptin25QD	−0.54 (−1.67, 0.57)	–	–	**−1.64 (−2.89, −0.40)**	–	2.64 (0.48, 16.94)	–			
Linagliptin2.5QD	−0.43 (−2.28, 1.43)	–	–	0.22 (−1.76, 2.21)	–	–	–			0.10 (0.00, 197.1)
Alogliptin12.5QD	–	–	–	0.95 (−0.92, 2.84)	–	1.14 (0.24, 5.84)	–			
Sitagliptin25QD	–	–	–	–	–	–	–	2.37 (0.19, 33.12)		
Sitagliptin100QD (reference)										
Vildagliptin50QD	−0.24 (−1.12, 0.64)	−0.28 (−1.46, 0.90)	−0.08 (−1.37, 1.24)	−0.02 (−1.28, 1.23)	–	1.24 (0.48, 3.20)	–	2.5 (0.28, 16.92)	–	–
Sitagliptin50QD	0.20 (−0.85, 1.26)	–	–	–	–	0.46 (0.12, 1.66)	–	1.07 (0.10, 9.44)	–	–
Saxagliptin5QD	0.30 (−0.40, 1.00)	0.06 (−0.55, 0.70)	−0.09 (−0.84, 0.66)	0.18 (−0.57, 0.92)	–	1.78 (0.69, 4.85)	–	–	–	–
Linagliptin5QD	−0.13 (−0.89, 0.63)	−0.02 (−0.72, 0.66)	**−14.30 (−15.50, −13.11)**	**−0.86 (−1.69, −0.02)**	–	0.75 (0.38, 1.44)	–	1.67 (0.37, 7.44)	0.70 (0.03, 15.93)	–
Linagliptin10QD	0.89 (−0.27, 2.04)	–	–	0.7 (−0.53, 1.93)	–	1.02 (0.15, 7.67)	–	1.62 (0.22, 13.90)	0.96 (0.01, 95.45)	–
Vildaglipt-in100QD	0.22 (−0.79, 1.24)	–	–	0.11 (−1.75, 1.95)	–	2.79 (0.64, 12.84)	–	2.77 (0.27, 28.99)	–	–
Linagliptin0.5QD	0.54 (−1.21, 2.31)	–	–	0.14 (−1.73, 2.01)	–	–	–	–	–	–
Alogliptin25QD	0.15 (−1.0, 1.32)	–	–	**−1.68 (−2.93, −0.43)**	–	2.32 (0.45, 13.48)	–	–	–	–
Linagliptin2.5QD	0.27 (−1.58, 2.10)	–	–	0.27 (−1.65, 2.18)	–	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	–	–	–	–	–	–

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Alogliptin12.5QD	–	–	–	1.00 (−0.84, 2.84)	–	–	–	–	–	–
Sitagliptin25QD	–	–	–	–	–	1.00 (0.23, 4.74)	–	3.53 (0.30, 48.53)	–	–
Vildagliptin50QD (reference)										
Sitagliptin50QD	0.44 (−0.72, 1.61)	–	–	–	–	–	–	–	–	–
Saxagliptin5QD	0.54 (−0.42, 1.51)	–	–	0.20 (−1.13, 1.52)	–	–	1.59 (0.32, 8.21)	–	–	–
Linagliptin5QD	0.11 (−0.84, 1.05)	–	**−14.23 (−15.88, −12.59)**	0.89 (−0.43, 2.19)	–	–	–	–	–	–
Linagliptin10QD	1.13 (−0.13, 2.38)	–	–	0.72 (−0.83, 2.29)	–	0.82 (0.13, 6.83)	–	0.64 (0.09, 7.15)	–	–
Vildaglipt-in100QD	0.46 (−0.60, 1.53)	–	–	0.13 (−1.62, 1.88)	−0.28 (−1.53, 0.99)	2.24 (0.56, 9.45)	0.60 (0.11, 2.97)	1.09 (0.21, 8.01)	–	–
Linagliptin0.5QD	0.79 (−1.04, 2.64)	–	–	0.16 (−1.93, 2.25)	–	–	–	–	–	0.33 (0.00, 119.7)
Alogliptin25QD	0.39 (−0.90, 1.65)	–	–	1,71 (0.11, 3.31)	0.65 (−0.93, 2.24)	1.89 (0.36, 10.85)	–	–	–	–
Linagliptin2.5QD	0.50 (−1.39, 2.40)	–	–	0.30 (−1.84, 2.44)	–	–	–	–	–	0.42 (0.00, 129.3)
Alogliptin12.5QD	–	–	–	1.02 (−1.06, 3.10)	0.34 (−1.47, 2.15)	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	0.61 (−1.54, 2.75)	–	–	–	–	–
Sitagliptin25QD	–	–	–	–	–	0.82 (0.17, 3.93)	–	–	–	–
Sitagliptin100QD	–	–	–	–	–	–	1.41 (0.34, 6.00)	–	–	–
Sitagliptin50QD (reference)										
Saxagliptin5QD	0.10 (−1.02, 1,22)	–	–	–	–	3.91 (0.87, 16.51)	–	–	–	–
Linagliptin5QD	−0.34 (−1.46, 0.78)	–	–	–	–	1.63 (0.47, 5.31)	–	1.56 (0.24, 11.53)	–	–
Linagliptin10QD	0.68 (−0.72, 2.08)	–	–	–	–	2.22 (0.25, 20.90)	–	1.52 (0.17, 17.59)	–	–

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Vildagliptin100QD	0.02 (−1.13, 1.18)	–	–	–	–	**6.02 (1.09, 33.66)**	–	2.59 (0.23, 34.28)	–	–
Linagliptin0.5QD	0.35 (−1.58, 2.29)	–	–	–	–	–	–	–	–	–
Alogliptin25QD	−0.06 (−1.30, 1.19)	–	–	–	–	5.04 (0.84, 35.42)	–	–	–	–
Linagliptin2.5QD	0.05 (−1.93, 2.06)	–	–	–	–	–	–	–	–	–
Vildagliptin50QD	–	–	–	–	–	2.67 (0.71, 10.00)	–	2.36 (0.23, 21.60)	–	–
Sitagliptin25QD	–	–	–	–	–	2.21 (0.52, 9.27)	–	–	–	–
Saxagliptin5QD (reference)										
Linagliptin5QD	−0.43 (−1.32, 0.45)	−0.09 (−0.92, 0.71)	**−14.21 (−15.55, −12.87)**	0.68 (−0.29, 1.64)		0.42 (0.15, 1.10)	–	–	–	–
Linagliptin10QD	0.58 (−0.64, 1.80)	–	–	0.52 (−0.78, 1.82)	–	0.57 (0.07, 4.85)	–	–	–	–
Vildagliptin100QD	−0.08 (−1.17, 1.01)	–	–	−0.07 (−1.96, 1.82)	–	1.57 (0.30, 8.19)	0.38 (0.04, 3.03)	–	–	–
Linagliptin0.5QD	0.25 (−1.55, 2.06)	–	–	−0.04 (−1.95, 1.88)	–	–	–	–	–	–
Alogliptin25QD	−0.16 (−1.38, 1.07)	–	–	1.51 (0.20, 2.82)	–	1.30 (0.21, 9.05)	–	–	–	–
Linagliptin2.5QD	−0.04 (−1.92, 1.84)	–	–	0.09 (−1.87, 2.07)	–	–	–	–	–	–
Alogliptin12.5QD	–	–	–	0.82 (−1.06, 2.70)	–	–	–	–	–	–
Vildagliptin50QD	–	–	–	–	–	0.70 (0.21, 2.21)	–	–	–	–
Sitagliptin25QD	–	–	–	–	–	0.56 (0.10, 3.08)	–	–	–	–
Linagliptin5QD (reference)										
Linagliptin10QD	1.02 (−0.11, 2.15)	–	–	−0.16 (−1.39, 1.07)	–	1.36 (0.22, 9.31)	–	0.97 (0.22, 5.24)	1.39 (0.03, 64.56)	0.58 (0.01, 30.43)
Vildagliptin100QD	0.36 (−0.72, 1.43)	–	–	−0.75 (−2.63, 1.14)	–	3.73 (0.89, 16.53)	–	1.67 (0.21, 13.69)	–	–

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Linagliptin0.5QD	0.68 (−1.08, 2.47)	–	–	−0.72 (−2.59, 1.365)	–		–	–	–	0.17 (0.00, 105.9)
Alogliptin25QD	0.28 (−0.95, 1.51)	–	–	0.83 (−0.51, 2.16)	–	3.10 (0.63, 17.41)	–	–	–	–
Linagliptin2.5QD	0.40 (−1.44, 2.24)	–	–	−0.58 (−2.52, 1.35)	–	–	–	–	–	0.21 (0.00, 124.6)
Alogliptin12.5QD	–	–	–	0.14 (−1.75, 2.04)	–	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	–	–	–	–	–	–
Vildagliptin50QD	–	–	–	–	–	1.65 (0.70, 4.05)	–	1.52 (0.22, 7.86)	–	0.49 (0.00, 487.6)
Sitagliptin25QD	–	–	–	–	–	1.34 (0.32, 6.09)	–	–	–	–
Linagliptin10QD (reference)										
Vildaglipt-in100QD	−0.66 (−1.02, 0.70)	–	–	−0.59 (−2.65, 1.47)	–	–	–	–	–	–
Linagliptin0.5QD	−0.34 (−2.03, 1.35)	–	–	−0.56 (−2.34, 1.21)	–	–	–	–	–	0.31 (0.00, 128.3)
Alogliptin25QD	−0.73 (−2.24, 0.76)	–	–	0.99 (−0.60, 2.57)	–	2.30 (0.19, 26.46)	–	–	–	–
Linagliptin2.5QD	−0.63 (−2.37, 1.13)	–	–	−0.43 (−2.24, 1.40)	–	–	–	–	–	0.38 (0.00, 138)
Alogliptin12.5QD	–	–	–	0.30 (−1.76, 2.37)	–	–	–	–	–	–
Vildagliptin100QD (reference)										
Linagliptin0.5QD	0.33 (−1.56, 2.23)	–	–	–	–	–	–	–	–	–
Alogliptin25QD	−0.08 (−1.32, 1.16)	–	–	–	0.93 (−0.42, 2.28)	0.84 (0.15, 4.92)	–	–	–	–
Linagliptin2.5QD	0.04 (−1.95, 2.01)	–	–	–	–	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	0.88 (−1.10, 2.86)	–	–	–	–	–
Linagliptin10QD	–	–	–	–	–	0.36 (0.04, 3.93)	–	0.59 (0.05, 7.38)	–	–
Linagliptin0.5QD (reference)										

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Alogliptin25QD	−0.41 (−2.41, 1.60)	–	–	1.55 (−0.57, 3.66)	–	–	–	–	–	–
Linagliptin2.5QD	−0.29 (−2.17, 1.60)	–	–	0.14 (−1.84, 2.10)	–	–	–	–	–	–
Vildaglipt-in100QD	–	–	–	−0.03 (−2.53, 2.46)	–	–	–	–	–	–
Alogliptin25QD (reference)										
Linagliptin2.5QD	0.12 (−1.94, 2.18)	–	–	–	–	–	–	–	–	–
Vildaglipt-in100QD	–	–	–	−1.58 (−3.67, 0.52)	–	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	–	–	–	–	–	–
Alogliptin12.5QD (reference)										
Linagliptin0.5QD	–	–	–	−0.86 (−3.36, 1.63)	–	–	–	–	–	–
Linagliptin2.5QD	–	–	–	−0.73 (−3.27, 1.82)	–	–	–	–	–	–
Alogliptin25QD	–	–	–	0.69 (−1.07, 2.44)	–	–	–	–	–	–
Linagliptin2.5QD (reference)										
Alogliptin25QD	–	–	–	1.42 (−0.74, 3.56)	0.32 (−0.95, 1.59)	–	–	–	–	–
Vildaglipt-in100QD	–	–	–	−0.17 (−2.70, 2.36)	−0.62 (−2.22, 1.00)	–	–	–	–	–
Vildagliptin50BID	–	–	–	–	0.26 (−1.65, 2.18)	–	–	–	–	–
Sitagliptin25QD (reference)										
Vildaglipt-in100QD	–	–	–	–	–	2.75 (0.40, 18.58)	–	0.79 (0.45, 12.42)	–	–
Linagliptin10QD	–	–	–	–	–	1.01 (0.96, 10.98)	–	0.47 (0.03, 6.19)	–	–
Vildagliptin50QD	–	–	–	–	–	–	–	**0.73 (4.40, 8.31)**	–	–
Alogliptin25QD	–	–	–	–	–	2.30 (0.30, 19.98)	–	–	–	–

Table 2 (continued)

Comparisons	HbA1c	2HPPG	BMI	FPG	Body weight	Hypoglycemia	Diarrhea	URTI	Renal and hepatic toxicity	Hypersensitivity reaction
Sitagliptin100QD (reference)										
Saxagliptin5QD	**1.13 (0.26, 5.36)**	–	–	–	–	–	1.13 (0.26, 5.36)	–	–	–
Vildagliptin100QD	**0.43 (0.06, 2.97)**	–	–	–	–	–	0.43 (0.06, 2.97)		–	–

Data of entries in bold type means significant results

Inconsistency check and model fit

Statistical inconsistency between the direct and indirect comparisons was generally low for 8 outcomes, the details of which are listed in Supplementary material A5. All loops were consistent because the 95% CIs included 1 according to the forest plots, indicating that the direct estimation of the summary effect does not differentiate from the indirect estimation. The summary estimations of the network meta-analysis are relatively robust. In addition, we added the plots on Bayesian model convergence in Supplementary material A6.

The model fit was evaluated using the posterior mean of the residual deviance $\bar{D}$res. The values of the $\bar{D}$res for the outcomes (HbA1c, FPG, 2HPPG, BMI, body weight, hypoglycemia, diarrhea, URTI, renal and hepatic toxicity and HR) were − 92.580, 224.709, 44.735, 28.842, 12.330, 269.932, 90.981, 124.087, 50.644 and 49.877, respectively, which were close to corresponding data point with − 90.430, 226.859, 46.885, 30.992, 14.480, 269.932, 90.981, 124.087, 50.644 and 49.877. The results showed that model's overall fit is relatively satisfactory.

Subgroup analysis and meta-regression

Finally, we included six studies [32, 33, 37, 51, 79, 82] (10.3%, 6/58) in Chinese language, we conducted subgroup analysis after removing them. The results are listed in Supplementary material A7. The data of HbA1c, FPG, 2HPPG, BMI, body weight and hypoglycemia (F) were analyzed again, except for the other outcomes without Chinese language. The result of removing studies with Chinese language is consistent with the previous results. The SUCRA showed that there was a difference rank of BMI, because of the small number of included studies after removing studies with Chinese language.

The results of meta-regression showed that there is no statistically significant difference in HbA1c related to mean age and disease duration with median treatment effect and the 95% credible interval for − 0.73 (− 2.23, 0.56) and − 0.72 (− 2.23, 0.58), respectively. In addition, there is no statistically significant difference in FPG related to disease duration with − 0.05 (− 0.83, 0.78) and mean age with − 0.09 (− 1.58, 0.05), respectively. We described the network meta-regression models in Supplementary material A8.

Discussion

This network meta-analysis investigated the efficacy and safety of different DPP4-I treatments (sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin) compared to placebo and compared different DPP4-I treatments with

Table 3 Ranking probability of different doses of DPP4-Is on outcomes

Treatment	HbA1c		FPG		2HPPG		BMI		Body weight		Hypoglycemia		Diarrhea		URTI		Renal and hepatic toxicity		HR	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Placebo	0.135	12	0.2719	12	0.1504	6	0.688	2	0.6571	2	0.6591	3	0.5543	3	0.6078	3	0.5137	2	0.5737	3
VIL50BID	0.8374	1	0.3453	9	0.3564	5	0.3404	5	0.3099	5	0.6187	4	0.4901	4	0.5668	4	0.3254	5	0.2621	7
SIT100QD	0.3884	9	0.3143	11	0.6881	2	0.4059	4	–	–	0.5252	7	0.3304	5	0.7567	1	0.496	4	–	–
VIL50QD	0.2493	11	0.3259	10	0.4132	4	0.4237	3	0.6004	3	0.4096	8	0.5583	2	0.3218	7	–	–	0.5247	4
SIT50QD	0.5148	7	–	–	–	–	–	–	–	–	0.1431	11	–	–	0.7028	2	–	–	–	–
SAX5QD	0.585	4	0.4236	6	0.746	1	0.1621	6	–	–	0.2436	9	0.2799	6	–	–	–	–	–	–
LIN5QD	0.3064	10	0.9338	1	0.6459	3	1	1	–	–	0.7431	2	–	–	0.4893	6	0.6616	1	0.3557	6
LIN10QD	0.8071	2	0.6585	4	–	–	–	–	–	–	0.5274	6	–	–	0.5111	5	0.5032	3	0.4912	5
VIL100QD	0.5303	5	0.4021	8	–	–	–	–	0.7954	1	0.8836	1	0.787	1	0.3008	8	–	–	–	–
LIN0.5QD	0.6448	3	0.4091	7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.6603	1
ALO25QD	0.4797	8	0.7434	2	–	–	–	–	0.2148	6	0.2163	10	–	–	–	–	–	–	–	–
LIN2.5QD	0.5218	6	0.4606	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.6323	2
ALO12.5QD	–	–	0.7115	3	–	–	–	–	0.4224	4	–	–	–	–	–	–	–	–	–	–
SIT25QD	–	–	–	–	–	–	–	–	–	–	0.5303	5	–	–	0.2428	9	–	–	–	–

BID twice daily, *QD* once daily, *SUCRA* surface under the cumulative ranking curve, *VIL* vildagliptin, *SIT* sitagliptin, *SAX* saxagliptin, *LIN* linagliptin, *ALO* alogliptin, *URTI* upper respiratory tract infection, *HR* hypersensitivity reaction

*Probability of being the best treatment, of being the second best, the third best, and so on, among treatments

each other. Recently, some network meta-analyses have demonstrated the clinical efficacy of GLP-1 RAs for type 2 diabetes [88, 89]. To the best of our knowledge, this is the first network meta-analysis to comprehensively estimate the efficacy and safety of different DPP4-I with dose distinction treatments for type 2 diabetes.

Network meta-analysis is a well-established research method for comparing different complex treatments [90]. In this systematic review and network meta-analysis, we investigated the direct and indirect evidence from 58 randomized controlled trials to compare 14 different interventions reported on 31,356 participants. Based on the common controlled treatments, our network meta-analysis allowed for indirect comparisons between the different DPP4-I treatments, synthesizing the indirect and direct results.

Glycemic level lowering effect

Our network meta-analysis suggested that except for alogliptin, a decrease was found for all DPP4-I versus the placebo for HbA1c. The SUCRA showed vildaglipti50BID and linagliptin10QD have the higher probability in reduction effect on HbA1c followed by linagliptin0.5QD; linagliptin5QD decreased the level of FPG most. The beneficial glycemic level lowering effect of all DPP4-I in our analysis was consistent with the results of previous studies [91, 92]. Singhfranco's study [93] found that linagliptin 5 mg/day for 12–24 weeks significantly reduced fasting plasma glucose (FPG) (− 1.01 mmol/l, $P < 0.00001$). But no significant differences were observed in the DPP4-I for 2HPPG in this network meta-analysis.

BMI and body weight lowering effect

Body weight gain is known to increase the risk of diabetes and diabetes-related complications [94], over 80% of individuals with T2DM are overweight or obese [95]. Overweight people are more likely to develop diabetes than others, weight loss interventions may be effective in reducing long-term diabetes risk even among overweight people [96]. Besides, BMI is a powerful and modifiable risk factor for diabetes [97]. Therefore, it is challenging for both doctors and patients to avoid the body weight gain and the rise of BMI of T2DM during treatment for glycemic control. Our network meta-analysis of SUCRA probabilities showed that vildagliptin5QD and linagliptin5QD had the highest probabilities for reducing the BMI and body weight, respectively.

Effect on adverse events

Hypoglycemia is a common complication of intensive diabetes therapy, possibly becoming an important risk factor for morbidity and mortality from T2DM [98]. Our network meta-analysis showed that sitagliptin50QD had the highest probabilities of SUCRA to become the most efficient treatment. These results were consistent with those of previous studies [99–101].

Up to 22% of the patients suffering diabetes mellitus may have diarrhea, and this may be caused by multiple factors, including neuropathy, adverse effects of anti-diabetic therapy [102]. In addition, the role of DPP-4 in immune functions, cell growth and apoptosis has raised certain level of concerns regarding a possible association with infections and hypersensitivity reactions. Our network meta-analysis results showed no significant reductions in incidence of diarrhea, renal and hepatic toxicity and hypersensitivity reaction; the SUCRA showed that the vildaglipti100QD, linagliptin5QD and linagliptin0.5QD had the lowest probabilities in reducing the incidence of them, respectively. With similar effect, our results may be helpful for clinicians in choosing DPP4-I with fewer gastrointestinal side effects for T2DM.

Sitagliptin100QD has the lowest probability in reducing the incidences of URTI, DPP4I have the similar effect in renal and hepatic toxicity, hypersensitivity reaction (HR). Although DPP4-I appear to have a good safety profile, they also have potential to cause adverse drug reactions (ADRs). Therefore, active pharmacovigilance should be carried out for risk identification and management. It is also important to motivate healthcare providers to understand their roles and responsibilities in the detection and management [103].

Strengths and limitations

Previous meta-analyses did not include even nearly the amount of trials of DPP4-I as the performed for this study, which is one of its principal improvements [104, 105]. Currently, as it is the most recommendable technique to confront various different treatments, the Bayesian model-based network meta-analysis allows to indirectly compare the various feasible treatments, even more when tests to directly compare different drugs for diabetes treatment are absent [106]. In addition, the network technique enables the estimation of the probability of whether one intervention is the best for one outcome. So it can provide an explicit ranking whenever many treatments are competing for one outcome. Our study provided the ranks of different doses of DPP4-I on outcomes for the first time.

There are several limitations in this network meta-analysis. Firstly, only trials in English and Chinese were included. Secondly, our results are based on the direct and indirect comparisons between therapies, so with the potential increase in the number of head-to-head trials in the future, some results may change. Thirdly, the results from risk of bias in individual studies indicate that a number of included studies are of low or unclear quality. Currently, the main factors resulting in unclear

quality include the random sequence generation, allocation concealment and other sources of bias. The other sources of bias also lead to the low quality; therefore, our future research is necessary to improve the quality of original research and avoid the occurrence of various bias risks. Fourthly, there is no description of the outcomes associated with pancreatitis in our included studies, so we failed to add this outcome into the manuscript. We look forward to more studies in relevant pancreatitis outcomes on DPP4-I safety. Fifthly, in the direct pairwise meta-analysis of individual DPP4-I with dose distinction, only one article (Garber 2008, [77]) about hypoglycemia was included. The sample size of this study is 515, which led to an extremely wide confidence interval. This is the possible reason why the confidence intervals for vildagliptin100QD are so wide (0.77–54.08).

Conclusion

DPP4-I have a lowering effect on the glycemic level (HbA1c, FPG), especially vildaglipti50BID and linagliptin10QD, respectively. Besides, linagliptin5QD has the greatest probabilities of reducing BMI. In addition, DPP4-I were associated with not increasing the incidence of adverse events. Among them, vildagliptin100QD and sitagliptin100QD have the lowest probability in reducing the incidence of hypoglycemia and URTI, respectively.

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Compliance with ethical standards

Conflict of interest The authors have indicated that they have no conflict of interest regarding the content of this article.

Human and animal rights statement This article is based on previously conducted studies and does not contain any studies with animals and humans performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Diabetes facts and figures. Brussels. International Diabetes Federation (2018). https://www.idf.org/ news/94:new-idf-figures-show-continued -increase-in-diabetes-across-the-globe,-reiterating-the-need-for-urgent-action.html. Accessed 1 Jan 2018
2. International Diabetes Federation. IDFDIABETESATLAS, 7th edn. http://www.idf.org/files/idf_publications/idf_diabetes_atlas_EN/idf_diabetes_atlas_EN/assets/common/downloads/publication.pdf. Accessed 01 Jan 2018
3. Deacon CF (2011) Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. Diabetes Obes Metab 13:17–18
4. Holst JJ, Deacon CF (1998) Inhibition of the activity of dipeptidyl peptidase IV as a treatment for type 2 diabetes. Diabetes 47:1663–1670
5. Thornberry NA, Weber AE (2007) Discovery of JANUVIA (sitagliptin), a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Curr Top Med Chem 7:557–568
6. Tahrani AA, Piya MK, Barnett AH (2009) Saxagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Adv Ther 26:249–262
7. Ckhardt ME, Angkop EL, Mark M et al (2007) 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3, 7-dihydro-1H-purine-2, 6-dione a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type-2 diabetes. Med Chem 50:6450–6453
8. Feng J, Zhang ZY, Wallace MB (2007) Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV. Med Chem 50:2297–2300
9. Gerrald KR, Van SE, Wines RC et al (2012) Saxagliptin and sitagliptin in adult patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 14(6):481–492
10. Wan LY, Zhang C, Guo WH et al (2013) Efficacy and safety of sitagliptin in patients with type 2 diabetes mellitus: a meta-analysis. Advers Drug React J 15(6):306–313
11. Ying L, Yu MZ, Xu XZ et al (2015) Efficacy and safety of linagliptin for type 2 diabetes mellitus: a meta-analysis. Chin J Evid Based Med 15(9):1068–1077
12. Bafeta A, Trinquart L, Seror R, Ravaud P (2014) Reporting of results from network meta-analyses: methodological systematic review. BMJ 348:g1741
13. Higgins JPT, Green S (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 [EB/OL]. The Cochrane Collaboration. http://www.cochrane-handbook.org. Accessed 3 Feb 2018
14. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
15. Chaimani A, Higgins JP, Mavridis D et al (2013) Graphical tools for network meta-analysis in STATA. PLoS One 8:e76654
16. Higgins JP, Altman DG (2008) Assessing risk of bias in included studies[M]/Cochrane handbook for systematic reviews of interventions: Cochrane book series. John Wiley, Hoboken, pp 187–241
17. Dersimonian R, Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 28(2):105
18. Hartung J, Knapp G (2001) A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med 20:3875–3889
19. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560. https://doi.org/10.1136/bmj.327.7414.557
21. Bulpitt C (1988) Subgroup analysis. Lancet 332(8601):31–34

22. Valkenhoef GV, Kuiper J (2016) Network meta-analysis using bayesian methods[M]/evidence synthesis for decision making in healthcare. John Wiley, Hoboken, pp 76–93
23. Lu G, Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 23:3105–3124
24. Dias S, Sutton AJ, Ades AE et al (2013) Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network metaanalysis of randomized controlled trials. Med Decis Making 33:607–617
25. Gelman A, Rubin DB (1992) Inference from iterative simulation using multiple sequences. Stat Sci 7:457–472
26. Salanti G, Ades AE, Ioannidis JP (2011) Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 64(2):163–171
27. Donegan S, Williamson P, D'Alessandro U, Tudur-Smith C (2013) Assessing key assumptions of network meta-analysis: a review of methods. Res Synth Methods 4:291–323
28. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A (2002) Bayesian measures of model complexity an fit. J R Stat Soc Ser B (Stat Methodol) 64:583–639
29. Tian JH, Zhang J, Ge L, Yang KH, Song FJ (2017) The methodological and reporting quality of systematic reviews from China and the USA are similar. J Clin Epidemiol 85:50–58
30. Xiaoyan C, Jing W, Xiaochun H, Yuyu T, Shunyou D, Yingyu F (2016) Effects of vildagliptin versus saxagliptin on daily acute glucose fluctuations in Chinese patients with T2DM inadequately controlled with a combination of metformin and sulfonylurea. Curr Med Res Opin 6:1–6
31. Koyanagawa N, Miyoshi H, Ono K et al (2016) Comparative effects of vildagliptin and sitagliptin determined by continuous glucose monitoring in patients with type 2 diabetes mellitus. Endocr J 63(8):747
32. Asti A, D'Alessandro A, Zito FP et al (2016) Sitagliptin versus saxagliptin in decompensated type 2 diabetes mellitus patients. Italian J Med 10(1):36
33. Huang HH, Xu WQ et al (2015) Comparative study on the efficacy of saxagliptin and vildagliptin in treating type 2 diabetes mellitus. Jiangxi Med J 2015(9):859–860
34. Chen P (2015) Clinical efficacy of DPP-IV inhibitor combined with metformin on type 2 diabetes mellitus. North Pharmaceutical (9):88–89
35. Tang YZ, Wang G, Jiang ZH et al (2015) Efficacy and safety of vildagliptin, sitagliptin, and linagliptin as add-on therapy in Chinese patients with T2DM inadequately controlled with dual combination of insulin and traditional oral hypoglycemic agent. Diabetol Metab Syndrome 7(1):91
36. Kothny W, Lukashevich V, Foley JE et al (2015) Comparison of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment: a randomised clinical trial. Diabetologia 58(9):2020–2026
37. Göke R, Eschenbach P, Dütting ED (2015) Efficacy of vildagliptin and sitagliptin in lowering fasting plasma glucose: results of a randomized controlled trial. Diabetes Metabol 41(3):244–247
38. Li LY, He X, Xie M et al (2014) Comparative study on the efficacy of Sitagliptin and saxagliptin in treating type 2 diabetes mellitus. 14(6):11–12.
39. Takihata M, Nakamura A, Terauchi Y et al (2014) Comparative study of three DPP-4 inhibitors, namely sitagliptin, vildagliptin, and alogliptin, in Japanese type 2 diabetic patients: the cosva randomized, controlled trial. Clin Diabetes Ther Posters 106:1024
40. Li CJ, Yu Q, Yu P et al (2014) Efficacy and safety comparison of add-on therapy with liraglutide, saxagliptin and vildagliptin, all in combination with current conventional oral hypoglycemic agents therapy in poorly controlled Chinese type 2 diabetes. Exp Clin Endocrinol Diabetes 122(8):469
41. Sakamoto M, Nishimura R, Irako T et al (2012) Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): crossover pilot study (J-VICTORIA study). Cardiovasc Diabetol 11(1):92
42. Rizzo MR, Barbieri M, Marfella R, Paolisso G (2012) Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. Pathophysiol Complicat 35(10):2076–2082
43. Guerci B, Monnier L, Serusclat P et al (2012) Continuous glucose profiles with vildagliptin versus sitagliptin in add-on to metformin: results from the randomized optima study. Diabetes Metab 38(4):359–366
44. Wang W, Yang J, Yang G et al (2016) Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: a multinational 24-week, randomized clinical trial. J Diabetes 8(2):229
45. Yang W, Xing X, Lv X et al (2015) Vildagliptin added to sulfonylurea improves glycemic control without hypoglycemia and weight gain in Chinese patients with type 2 diabetes mellitus. J Diabetes 7(2):174
46. Sheu WHH, Park SW, Yan G et al (2015) Linagliptin improves glycemic control after 1 year as add-on therapy to basal insulin in Asian patients with type 2 diabetes mellitus. Curr Med Res Opin 31(3):1–34
47. Schmieder RE, Friedrich S, Kistner I et al (2015) Effects of linagliptin on early alterations of renal endothelial function in patients with type-2 diabetes. Nephrol Dial Transplant 30(suppl_3):iii11
48. Chantal M, Ravi SR, Daniel L et al (2015) A randomized clinical trial to evaluate the efficacy and safety of co-administration of sitagliptin with intensively titrated insulin glargine. Diabetes Ther 6(2):127
49. Leibowitz G, Cahn A, Bhatt DL et al (2015) Impact of treatment with saxagliptin on glycaemic stability and β-cell function in the SAVOR-TIMI 53 study. Diabetes Obes Metab 17(5):487
50. Laakso M, Rosenstock J, Groop PH et al (2015) Treatment with the dipeptidyl peptidase-4 inhibitor linagliptin or placebo followed by glimepiride in patients with type 2 diabetes with moderate to severe renal impairment: a 52-week, randomized, double-blind clinical trial. Diabetes Care 38(2):15–17
51. Kohei K, Takashi K, Yasuo T et al (2015) Sitagliptin improves glycemic excursion after a meal or after an oral glucose load in Japanese subjects with impaired glucose tolerance. Diabetes Obes Metab 17:11
52. Wu YF (2013) The effect of saxagliptin monotherapy on treating new type 2 diabetes. Doctoral dissertation, Zhejiang University
53. Yang W, Guan Y, Yue S et al (2012) The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. J Diabetes 4(3):227–237
54. Rauch T, Graefe-Mody U, Deacon CF et al (2012) Linagliptin increases incretin levels, lowers glucagon, and improves glycemic control in type 2 diabetes mellitus. Diabetes Ther 3(1):10
55. Pan CY, Yang W, Tou C et al (2011) Efficacy and safety of saxagliptin in drug-naïve Asian patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract 28(3):217–224
56. Pan C, Xing X, Han P et al (2012) Efficacy and tolerability of vildagliptin as add-on therapy to metformin in Chinese patients with type 2 diabetes mellitus. Diabetes Obes Metab 14(8):737–744
57. Minervini G, Iqbal N, Charbonnel B et al (2012) Efficacy and safety of saxagliptin in combination with insulin in patients with long-standing type 2 diabetes. Intern Med J 61:A290

58. Kothny W, Shao Q, Groop P et al (2012) One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes Obes Metab 14(11):1032–1039
59. Kawamori R, Inagaki N, Araki E et al (2011) Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. Diabetes Obes Metab 14(4):348–357
60. Gerosa D, Ragonesi PD, Anna C et al (2012) Vildagliptin action on some adipocytokine levels in type 2 diabetic patients: a 12-month, placebo-controlled study. Expert Opin Pharmacother 13(18):2581–2591
61. Derosa G, Carbone A, Franzetti I et al (2012) Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, β-cell function and insulin resistance in type 2 diabetic patients. Diabetes Res Clin Pract 98(1):51–60
62. Barnett A, Huisman H, Jones R et al (2012) Efficacy and safety of linagliptin in elderly patients (≥ 70 Years) with type 2 diabetes. Can J Diabetes 36(5):S39
63. Tajima N, Kadowaki T, Odawara M et al (2011) Addition of sitagliptin to ongoing glimepiride therapy in Japanese patients with type 2 diabetes over 52 weeks leads to improved glycemic control. Diabetol Int 2(1):32–44
64. Seino Y, Fujita T, Hiroi S et al (2011) Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. Curr Med Res Opin 27(9):1781–1792
65. Del PS, Barnett AH, Huisman H et al (2011) Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab 13(3):258
66. Nowicki M, Rychlik I, Haller H et al (2011) Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab 13(6):523
67. Nowicki M, Rychlik I, Haller H et al (2011) Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract 65(12):1230
68. Mcgill JB, Sloan L, Newman J et al (2013) Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment. A 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care 36(2):237
69. Lukashevich V, Schweizer A, Shao Q et al (2011) Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes Obes Metab 13(10):947–954
70. Lukashevich V, Schweizer A, Foley J, Shao Q, Groop PH, Kothny W et al (2011) Efficacy of vildagliptin therapy in combination with insulin in patients with type 2 diabetes and severe renal impairment. Diabetologia 54(Suppl1):S332
71. Kothny W, Schweizer A, Naik R, Groop PH, Shao Q, Lukashevich V et al (2011) Comparison of vildagliptin with placebo in a 24-week study of 221 patients with type 2 diabetes and severe renal impairment (eGFR < 30). Diabetologia. 54(Suppl1):S332
72. Newman J, Mcgill JB, Patel S, Friedrich C, Sauce C, Woerle HJ et al (2011) Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment. Diabetologia 54(Suppl1):S333
73. Horie Y, Kanada S, Watada H et al (2011) Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor linagliptin: a 4-week multicenter, randomized, double-blind, placebo-controlled phase IIa study in Japanese type 2 diabetes patients. Clin Ther 33(7):973
74. Dandona P, Makdissi A, Chang S et al (2011) Sitagliptin exerts an anti-inflammatory effect. Am Diabetes Assoc 60:A306
75. Barzilai N, Guo H, Mahoney EM et al (2011) Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 27(5):1049–1058
76. Garber AJ, Foley JE, Banerji MA et al (2010) Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea. Diabetes Obes Metab 10(11):1047–1056
77. Defronzo RA, Fleck PR, Wilson CA et al (2008) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care 31(12):2315–2317
78. Chan JC, Scott R, Arjona Ferreira JC et al (2008) Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab 10(7):545–555
79. Su Y, Lv LF, Li QZ, Zhao ZG (2014) A randomized controlled clinical trials for the treatment of type 2 diabetes by vildagliptin and alpha-glucosidase inhibitor. Chin J New Drugs 22:2655–2658
80. Lukashevich V, Kozlovski P, Foley J, Kothny W et al (2012) Vildagliptin combined with insulin reduces HBA1C without increasing risk of hypoglycemia and weight gain in patients with type 2 diabetes mellitus. Diabetes 61:A254
81. Moses RG, Kalra S, Brook D, Sockler J, Visvanathan J, Fisher SA (2012) Saxagliptin (SAXA) effectively reduces HbA1c and is well tolerated when added to a combination of metformin (MET) and sulfonylurea (SU). Clin Diabetes/Ther Posters 61:A282
82. Su Y, Lv LF, Li QZ, Zhao ZG, Su YL (2014) The clinical research on the treatment of type 2 diabetes mellitus by DPP-4 inhibitor. Chin J Diabetes 22(10):886–889
83. Ba J, Han P, Yuan G et al (2017) Randomized trial assessing the safety and efficacy of sitagliptin in Chinese patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or combined with metformin. J Diabetes 09:667–676
84. Pan C, Han P, Ji Q, li C, Lu J et al (2017) Efficacy and safety of alogliptin in patients with type 2 diabetes mellitus: a multicentre randomized double-blind placebo-controlled phase 3 study in mainland China, Taiwan, and Hong Kong. J Diabetes 09:386–395
85. Shah A, Levesque K, Pierini E et al (2017) Effect of sitagliptin on glucose control in type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery. Diabetes Obes Metab 20:1–6
86. Tanaka K, Okada Y, Mori H et al (2017) Comparative analysis of the effects of alogliptin and vildagliptin on glucose metabolism in type 2 diabetes mellitus. Endocr J 64(2):179–189
87. Wang W, Ning G, Ma J et al (2017) A randomized clinical trial of the safety and efficacy of sitagliptin in patients with type 2 diabetes mellitus inadequately controlled by acarbose alone. Curr Med Res Opin 33(4):693–699
88. Sun F, Wu S, Guo S et al (2015) Effect of GLP-1 receptor agonists on waist circumference among type 2 diabetes patients: a systematic review and network meta-analysis. Endocrine 48(3):794–803
89. Sun F, Wu S, Guo S et al (2015) Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Res Clin Pract 10(1):26–37
90. Jansen JP, Fleurence R, Devine B et al (2011) Interpreting indirect treatment comparisons and network meta-analysis for healthcare decision making: report of the ISPOR task force on indirect

treatment comparisons good research practices: part 1. Value Health 14(4):417–428
91. Cai L, Cai Y, Lu ZJ et al (2012) The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. J Clin Pharm Ther 37(4):386
92. Bekiari E, Rizava C, Athanasiadou E et al (2015) Systematic review and meta-analysis of vildagliptin for treatment of type 2 diabetes. Endocrine 52(3):458–480
93. Singhfranco D, Mclaughlinmiddlekauff J, Elrod S et al (2012) The effect of linagliptin on glycaemic control and tolerability in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 14(8):694–708
94. Bryzinski BHB (2015) A pooled analysis of the efficacy and safety of saxagliptin as monotherapy in patients with type 2 diabetes. J Diabetes Metab 06:4
95. Shin S-J (2012) Glucagon-like peptide-1 receptor agonists and their effects on weight reduction. J Diabetes Investig 03:490–491
96. Resnick HE, Valsania P, Halter JB et al (2000) Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Commun Health 54(8):596–602
97. Ford ES, Williamson DF, Liu S (1997) Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol 146:214–222
98. Moghissi E, Ismailbeigi F, Devine RC (2013) Hypoglycemia: minimizing its impact in type 2 diabetes. Endocr Pract 19(3):1–33
99. Mbanya JC, Al-Sifri S, Abdel-Rahim A et al (2015) Incidence of hypoglycemia in patients with type 2 diabetes treated with gliclazide versus DPP-4 inhibitors during Ramadan: a meta-analytical approach. Diabetes Res Clin Pract 109(2):226–232
100. Kim HM, Lim JS, Lee BW et al (2015) Optimal candidates for the switch from glimepiride to sitagliptin to reduce hypoglycemia in patients with type 2 diabetes mellitus. Endocrinol Metab 30(1):84–91
101. Phung OJ, Scholle JM, Talwar M et al (2010) Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain and hypoglycemia in Type 2 diabetes. JAMA 303(14):1410–1418
102. Zhao Q, Hong D, Zheng D et al (2014) Risk of diarrhea in patients with type 2 diabetes mellitus treated with sitagliptin: a meta-analysis of 30 randomized clinical trials. Drug Des Dev Ther 8:2283
103. Bhattacharjee A, Gupta MC, Agrawal S (2016) Adverse drug reaction monitoring of newer oral anti-diabetic drugs—a pharmacovigilance perspective. Int J Pharmacol Res 6(04):142–151
104. Esposito K, Chiodini P, Maiorino MI et al (2014) Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials. BMJ Open 4(6):e005442–e005442
105. Karagiannis T, Paschos P, Paletas K et al (2012) Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 344:449–449
106. Caldwell DM, Ades AE, Higgins JPT (2005) Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331(7521):897–900

Affiliations

Juan Ling[1,2,3,4] · Peng Cheng[5] · Long Ge[1,2,3,4,6] · Ding-hua Zhang[7] · An-chen Shi[8] · Jin-hui Tian[1,2,3,4] · Ya-jing Chen[9] · Xiu-xia Li[1,2,3,4] · Jing-yun Zhang[1,2,3,4] · Ke-hu Yang[1,2,3,4]

1 Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China

2 Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province, Lanzhou 730000, China

3 Chinese GRADE Center, Lanzhou University, Lanzhou 730000, China

4 WHO Collaborating Center for Guideline Implementation and Knowledge Translation, Lanzhou 730000, China

5 Department of Orthopedics, The Second Hospital of Lanzhou University, Lanzhou, China

6 First Clinical Medical College of Lanzhou University, Lanzhou 730000, China

7 Department of Endocrinology, Gansu Province Hospital of Traditional Chinese Medicine, Lanzhou, China

8 Second Clinical Medical College of Lanzhou University, Lanzhou 730000, China

9 School of Public Health of Lanzhou University, Lanzhou 730000, Gansu, China