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BRIEF REPORT

Direct head-to-head comparison of glycaemic durability of dipeptidyl peptidase-4 inhibitors and sulphonylureas in patients with type 2 diabetes mellitus: A meta-analysis of long-term randomized controlled trials

Kang Chen MD[1] | Deying Kang MSc[2] | Miao Yu PhD[3] | Ruya Zhang MD[4] | Ye Zhang MD[4] | Guojuan Chen MD[4] | Yiming Mu MD[1] (iD)

[1]Department of Endocrinology, Chinese PLA General Hospital, Beijing, China

[2]Department of Evidence-based Medicine and Clinical Epidemiology, West China Hospital, Sichuan University, Chengdu, China

[3]Department of Endocrinology, Key Laboratory of Endocrinology, Ministry of Health, Peking Union Medical College Hospital, Diabetes Research Centre of Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[4]Medical Affairs, MSD China Holding Company, Shanghai, China

Correspondence
Dr Yiming Mu, Department of Endocrinology, Chinese PLA General Hospital, Beijing, 100853 China.
Email: muyiming@301hospital.com.cn

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MSD China Holding Co., Ltd.

We performed a meta-analysis of randomized controlled trials (RCTs) to compare the long-term glycaemic durability of dipeptidyl-peptidase 4 (DPP-4) inhibitors vs that of sulphonylureas (SUs) in patients with type 2 diabetes mellitus (T2DM), in terms of the changes in glycated haemoglobin (HbA1c) levels from an intermediate time point (26 or 52 weeks) to 104 weeks of treatment. The Medline (PubMed), Embase (Ovid), and CENTER (Cochrane Library) databases were searched for relevant RCTs. Eight RCTs were included. Compared with SUs, DPP-4 inhibitors were associated with significantly smaller increases in the HbA1c level from 24 to 28 weeks to 104 weeks (mean difference [MD]: −0.16%, 95% confidence interval [CI]: −0.21 to −0.11; $P < .001$) and from 52 weeks to 104 weeks (MD −0.06%, 95% CI −0.10 to −0.02; $P = .001$). No significant heterogeneities were detected among the included comparisons ($I^2 = 0\%$). These results suggest that long-term treatment with DPP-4 inhibitors confers better durability of glycaemic response than treatment with SUs in patients with T2DM, which may indicate that DPP-4 inhibitors better preserve islet β-cell function compared with SUs.

KEYWORDS

dipeptidyl peptidase-4 inhibitors, glycaemic durability, glycated haemoglobin, meta-analysis, sulphonylureas

1 | INTRODUCTION

Sulphonylureas (SUs) are conventionally chosen as the treatment for type 2 diabetes mellitus (T2DM) after metformin failure[1]; however, the glucose-lowering effect of SUs tends to diminish as a function of time. Dipeptidyl peptidase-4 (DPP-4) inhibitors, a novel class of OADs that function to inhibit the DPP-4 enzyme-induced degradation of glucagon-like peptide-1, have become a widely accepted option for T2DM treatment in the past decade.[2] Regarding the long-term efficacy of DPP-4 inhibitors for glycaemic control, although a recent meta-analysis combining the results of long-term clinical trials suggested that the effect of DPP-4 inhibitors on glycated haemoglobin (HbA1c) levels in patients with T2DM may decline during the second year of treatment,[3] conclusive results have not been obtained. More importantly, the results of pilot studies evaluating the comparative glycaemic durability of DPP-4 inhibitors and SUs were not consistent[4–11]; therefore, the aim of the present study was to perform a meta-analysis of long-term randomized controlled trials (RCTs) to compare the glycaemic durability of DPP-4 inhibitors and SUs in patients with T2DM, as reflected by the change in HbA1c levels from an intermediate time point (26 or 52 weeks) to 104 weeks of treatment.

2 | METHODS

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[12] and the Cochrane Handbook guidelines.[13]

Kang Chen and Deying Kang are co-first authors.

2.1 | Search strategy

The Medline (PubMed), Embase (Ovid), and CENTER (Cochrane Library) databases were systematically searched using the terms "DPP4," "DPP-4," "dipeptidyl peptidase-4 inhibitors," "sitagliptin," "vildagliptin," "linagliptin," "saxagliptin," "alogliptin," "dutogliptin," "aemigliptin," "anagliptin," "teneligliptin," "trelagliptin," or "omarigliptin" coupled with "glimepiride," "glipizide," "gliclazide," "glibenclamide," "glyburide," "gliguidone," "sulphonylureas," "sulfonylureas," and "random," "randomly," or "randomized." The final search was performed on January 25, 2017. The search was limited to clinical trials in humans. We also manually analysed the references of original and review articles to identify additional studies.

2.2 | Criteria for study selection

Studies were included if they: (1) were full-length articles in English or Chinese; (2) were RCTs with a parallel design; (3) recruited people with confirmed T2DM; (4) assigned patients to either an oral DPP-4 inhibitor treatment group or an oral SU group; (5) had a treatment duration of at least 2 years (104 weeks); and (6) provided information necessary for extraction or estimation of data for changes in HbA1c levels from an intermediate time point (26 or 52 weeks) to 104 weeks.

2.3 | Data extraction and quality assessment

Two authors independently performed the literature search, data extraction and quality assessment. Discrepancies were resolved by discussion with the corresponding author. The Cochrane Risk of Bias Tool with seven domains[13] was applied for study quality evaluation.

2.4 | Statistical analysis

REVMAN (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software (version 12.0; Stata Corporation, College Station, Texas) were used for statistical analysis. The primary outcome of this meta-analysis was the change in HbA1c level from an intermediate time point (26 or 52 weeks) to 104 weeks of treatment with DPP-4 inhibitors and SUs. If data for HbA1c levels at a certain intermediate time point were not reported, data for the nearest time-point were used. The combined effect was presented as a mean difference (MD) with the 95% confidence interval (CI). Heterogeneity was evaluated with Cochrane's Q test,[13] and significant heterogeneity was considered if $P < .10$. The I^2 statistic was determined to describe the percentage of total variation across studies. A random effects model was used because it is a more conservative method which considers heterogeneity among the included studies.[13] Data from studies with more than one interventional arm with DPP-4 inhibitors were considered as multiple comparisons and were included in the meta-analysis after the sample sizes of the control groups had been equally split, as indicated by the Cochrane Handbook guideline.[13] Publication bias was assessed by visual inspection of the asymmetry of the funnel plot and Egger's regression asymmetry test.[13] P values were two-tailed, and statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Study selection

A flow chart outlining the study selection process is presented in Figure S1. A final total of eight RCTs were included in our study.[4–11]

3.2 | Study characteristics and quality evaluation

Of the eight included RCTs, one included two interventional arms with different doses of alogliptin (12.5 and 25 mg once daily), and these were included as two comparisons. The clinical and baseline patient characteristics for the included studies are presented in Table 1. All of the RCTs included patients already taking metformin, except for one study that included medication-naïve patients,[4] and there was considerable variation in HbA1c levels at baseline (7.5%-11.0%). Different DPP-4 inhibitors were used, including vildagliptin, sitagliptin, alogliptin, linagliptin and saxagliptin. The drop-out rate was substantial for the included RCTs, and the strategies of considering observed cases and last observation carried forward were applied to handle this issue. The details of the quality evaluation are shown in Table S1. All of the included studies were double-blind RCTs.

3.3 | Comparative glycaemic durability of DPP-4 inhibitors and SUs

Treatment with DPP-4 inhibitors was associated with significantly smaller changes in HbA1c levels from 24 to 28 weeks to 104 weeks (MD −0.16%, 95% CI −0.21 to −0.11; $P < .001$; Figure 1A) and 52 weeks to 104 weeks (MD −0.06%, 95% CI −0.10 to −0.02; $P = .001$; Figure 1B) compared with SUs, with no considerable heterogeneity ($I^2 = 0\%$). A sensitivity analysis based on the omission of the study including medication-naïve patients showed similar results (24-28 weeks: MD −0.15%, 95% CI −0.20 to −0.10, $P < .001$; 52 weeks: MD −0.06%, 95% CI −0.10 to −0. 02, $P = .003$).

3.4 | Publication bias

The funnel plots for the comparative effectiveness of DPP-4 inhibitors and SUs for long-term glycaemic control (Figure S2) were symmetrical on visual inspection, suggesting no significant publication bias. Egger's significance test also did not indicate the existence of publication bias ($P = .542$ and $P = .388$, respectively).

4 | DISCUSSION

The present meta-analysis showed that treatment of patients with T2DM with DPP-4 inhibitors was associated with a significantly smaller change in the HbA1c level from an intermediate time point to the end of 104 weeks of follow-up as compared with treatment with SUs, suggesting that DPP-4 inhibitors offer better glycaemic durability than SUs. Considering the other advantages of DPP-4 inhibitors over SUs, such as the lower incidence of adverse events, including hypoglycaemia, and the lesser impact on body weight, the results of the present study indicate that DPP-4 inhibitors might be a preferable treatment choice for patients with T2DM as an add-on medication with metformin.

TABLE 1 Baseline patient and clinical characteristics of the included studies

Study	Design	N	Mean age, years	Sex, % men	BMI, kg/m^2	Baseline HbA1c, %	T2DM duration, years	Add-on therapy	Extension study	DPP-4 inhibitor dose	SU dose	Intermediate time point, weeks	Final time point, weeks	Drop out, %, and handling strategy
Foley 2009	R, DB	811	54.8	55.8	30.7	8.7	2.2	N	N	Vildagliptin, 50 mg twice daily	Gliclazide, 80-320 mg once daily	24, 52	104	25.7%, LOCF
Ahren 2010	R, DB	258	57.5	53.6	31.8	7.3	5.7	Y, Metformin	Y	Vildagliptin, 50 mg twice daily	Glimepiride, 2-6 mg once daily	24, 52	104	NR
Matthews 2010	R, DB	1357	57.5	53.5	31.6	7.2	5.7	Y, Metformin	N	Vildagliptin, 50 mg twice daily	Glimepiride, 2-6 mg once daily	24, 53	104	37.6%, LOCF
Seck 2010	R, DB	504	57.3	60.1	31.1	7.3	5.8	Y, Metformin	N	Sitagliptin, 100 mg once daily	Glipizide, 5-20 mg once daily	24, 54	104	56%, OC
Gallwitz 2012	R, DB	504	59.8	60.5	30.3	7.7	NR	Y, Metformin	N	Linagliptin, 5 mg once daily	Glimepiride, 1-4 mg once daily	28, 52	104	23%, LOCF
Goke 2013	R, DB	312	57.5	52.4	31.4	7.7	5.5	Y, Metformin	Y	Saxagliptin, 5 mg once daily	Glipizide, 5-20 mg once daily	24, 52	104	73%, LOCF
Ahren 2014	R, DB	602	55.1	50.1	NR	8.2	6.2	Y, Metformin	N	Sitagliptin, 100 mg once daily	Glimepiride, 2-4 mg once daily	24, 52	104	33%, LOCF
Del 2014, 12.5 mg	R, DB	1317	55.4	48.9	31.2	7.6	5.6	Y, Metformin	N	Alogliptin, 12.5 mg once daily	Glipizide, 5-20 mg once daily	26, 52	104	22%, LOCF
Del 2014, 25 mg	R, DB	1322	55.4	50.8	31.2	7.6	5.5	Y, Metformin	N	Alogliptin, 25 mg once daily	Glipizide, 5-20 mg once daily	26, 52	104	22%, LOCF

Abbreviations: BMI, body mass index; DB, double-blind; LOCF, last observation carried forward; N, no; NR, not reported; OC, observed cases; R, randomized; Y, yes.
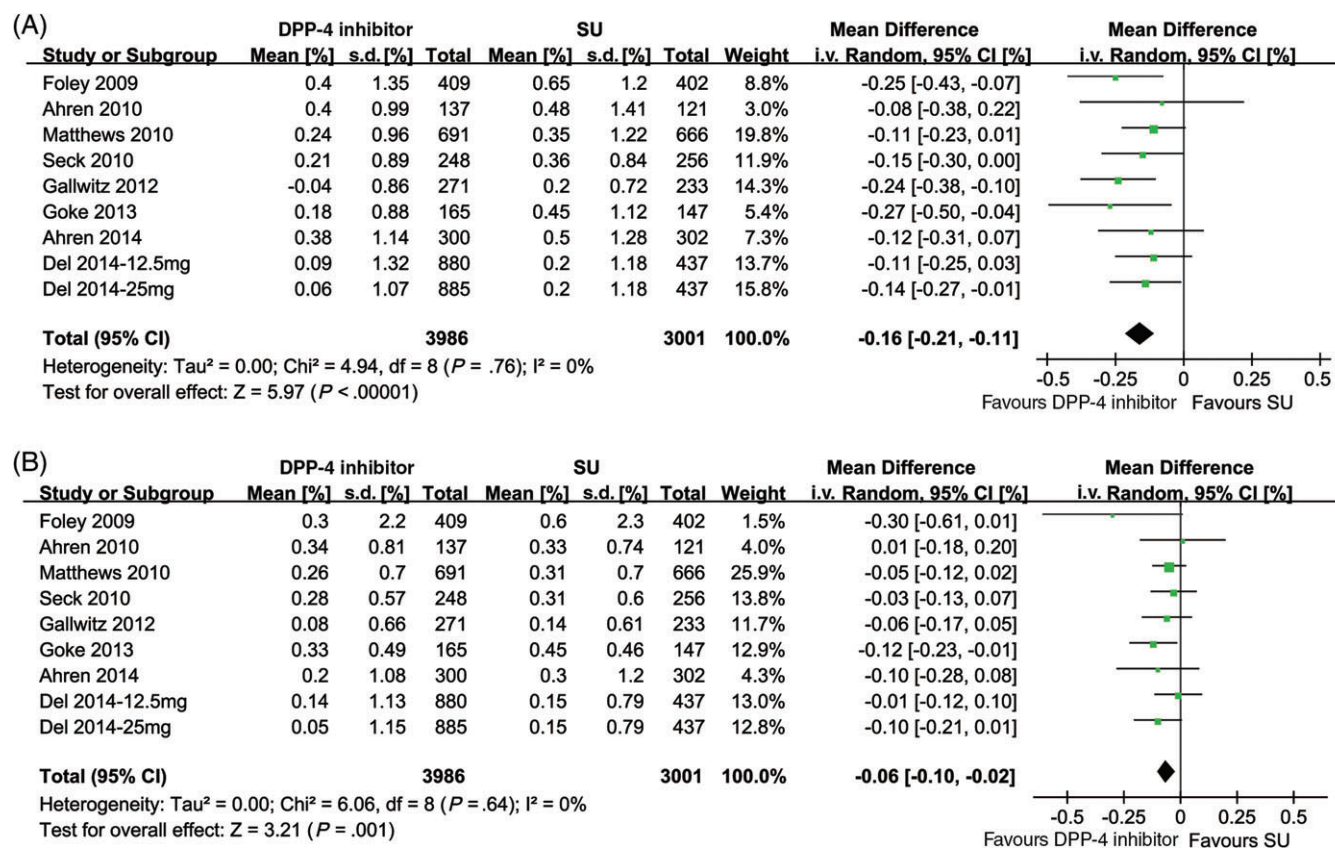
(A)

Study or Subgroup	DPP-4 inhibitor Mean [%]	s.d. [%]	Total	SU Mean [%]	s.d. [%]	Total	Weight	Mean Difference i.v. Random, 95% CI [%]
Foley 2009	0.4	1.35	409	0.65	1.2	402	8.8%	-0.25 [-0.43, -0.07]
Ahren 2010	0.4	0.99	137	0.48	1.41	121	3.0%	-0.08 [-0.38, 0.22]
Matthews 2010	0.24	0.96	691	0.35	1.22	666	19.8%	-0.11 [-0.23, 0.01]
Seck 2010	0.21	0.89	248	0.36	0.84	256	11.9%	-0.15 [-0.30, 0.00]
Gallwitz 2012	-0.04	0.86	271	0.2	0.72	233	14.3%	-0.24 [-0.38, -0.10]
Goke 2013	0.18	0.88	165	0.45	1.12	147	5.4%	-0.27 [-0.50, -0.04]
Ahren 2014	0.38	1.14	300	0.5	1.28	302	7.3%	-0.12 [-0.31, 0.07]
Del 2014-12.5mg	0.09	1.32	880	0.2	1.18	437	13.7%	-0.11 [-0.25, 0.03]
Del 2014-25mg	0.06	1.07	885	0.2	1.18	437	15.8%	-0.14 [-0.27, -0.01]
Total (95% CI)			**3986**			**3001**	**100.0%**	**-0.16 [-0.21, -0.11]**

Heterogeneity: Tau² = 0.00; Chi² = 4.94, df = 8 (P = .76); I² = 0%
Test for overall effect: Z = 5.97 (P < .00001)

Favours DPP-4 inhibitor   Favours SU

(B)

Study or Subgroup	DPP-4 inhibitor Mean [%]	s.d. [%]	Total	SU Mean [%]	s.d. [%]	Total	Weight	Mean Difference i.v. Random, 95% CI [%]
Foley 2009	0.3	2.2	409	0.6	2.3	402	1.5%	-0.30 [-0.61, 0.01]
Ahren 2010	0.34	0.81	137	0.33	0.74	121	4.0%	0.01 [-0.18, 0.20]
Matthews 2010	0.26	0.7	691	0.31	0.7	666	25.9%	-0.05 [-0.12, 0.02]
Seck 2010	0.28	0.57	248	0.31	0.6	256	13.8%	-0.03 [-0.13, 0.07]
Gallwitz 2012	0.08	0.66	271	0.14	0.61	233	11.7%	-0.06 [-0.17, 0.05]
Goke 2013	0.33	0.49	165	0.45	0.46	147	12.9%	-0.12 [-0.23, -0.01]
Ahren 2014	0.2	1.08	300	0.3	1.2	302	4.3%	-0.10 [-0.28, 0.08]
Del 2014-12.5mg	0.14	1.13	880	0.15	0.79	437	13.0%	-0.01 [-0.12, 0.10]
Del 2014-25mg	0.05	1.15	885	0.15	0.79	437	12.8%	-0.10 [-0.21, 0.01]
Total (95% CI)			**3986**			**3001**	**100.0%**	**-0.06 [-0.10, -0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 6.06, df = 8 (P = .64); I² = 0%
Test for overall effect: Z = 3.21 (P = .001)

Favours DPP-4 inhibitor   Favours SU

FIGURE 1 Forest plots for the comparative glycaemic durability of DPP-4 inhibitors and SUs. A, Changes in HbA1c levels from 24 to 28 to 104 weeks of treatment; B, changes in HbA1c levels from 52 to 104 weeks of treatment. i.v., intravenous; s.d., standard deviation

Diminished β-cell function has been recognized as an important step in the pathogenesis of T2DM.[14] Insulin resistance, as an initial event during the pathogenesis of T2DM, leads to accelerated insulin secretion by islet β cells, which eventually results in the overwork of the β cells and subsequent deterioration of β-cell function.[15] Because the primary pharmacological effects of SUs are the stimulation of insulin secretion by β cells, the significant glucose-lowering effect that can be observed during the early phase of the treatment eventually fades or even disappears with long-term treatment. This so-called monotherapy failure with SUs has been linked to continuous loss of functional islet β cells and impaired β-cell function during the progression of T2DM.[16] Our finding that DPP-4 inhibitors have better glycaemic durability than SUs is consistent with the results of previous studies demonstrating that DPP-4 inhibitors may have beneficial effects on the preservation of β-cell numbers and β-cell functions. An early study in rats with streptozotocin-induced diabetes found that the DPP-4 inhibitor P32/98 had a dose-dependent preventive effect on streptozotocin-induced β-cell apoptosis, suggesting that the therapeutic effects of DPP-4 inhibitors may involve the prevention of functional β-cell loss.[17] By contrast, treatment with glipizide, was not associated with restoration of β-cell mass.[18] Subsequent experimental studies also indicated that some DPP-4 inhibitors had protective effects on β-cell mass and function.[19] These results suggest that the preservation of β-cell mass and function is a common effect of DPP-4 inhibitors. Further studies are needed to confirm our hypothesis that DPP-4 inhibitors confer better protective effects on β-cell mass and function in humans, particularly as compared with SUs.

Our results have limitations that should be considered when interpreting the results. First, we tested our hypothesis that DPP-4 inhibitors offer better glycaemic durability than SUs using the change in the HbA1c level from an intermediate time point to the final time point as the outcome. To minimize the influence of the choice of the intermediate time point on the meta-analysis results, we chose two intermediate time points (26 and 52 weeks) for evaluation. Since a generalized index for glycaemic durability is lacking for current medical research, our approach may be a practical method for evaluating glycaemic durability of OADs in diabetes research. As mentioned in a previous meta-analysis with the outcome of glycaemic durability[3] and the curves of treatment effects of our included RCTs,[4-11] the maximum reduction in HbA1c by DPP-4 inhibitors appeared at ~24 to 28 weeks after the initiation of the treatment; therefore, it is logical to evaluate the glycaemic durability after the stabilization of the DPP-4 inhibitors' therapeutic effects. In addition, our conclusions were confirmed by the consistent results obtained for changes in HbA1c levels from two intermediate time points to the final visit. Secondly, the difference in treatment effect size was not particularly large, and the clinical relevance of the results deserves further confirmation; however, because HbA1c is a relatively stable variable that is considered a reflection of glucose levels within 3 months and has been linked to the risk of diabetes complications, the results of our study may indicate the benefits of long-term administration of DPP-4 inhibitors over SUs on clinical outcome. Thirdly, the total follow-up duration was limited to 104 weeks. Obviously, changes in glycaemic control after treatment with DPP-4 inhibitors vs SUs beyond the 2-year duration deserve further investigation. Fourthly, our study included two

extension studies based on original studies with a 52-week follow-up, which may introduce selection bias because patients with unsatisfactory glucose control during follow-up for the original studies may not have participated in the extension studies; however, a meta-analysis limited to studies originally designed with a 104-week follow-up produced similar results. Fifthly, the participant drop-out rates varied among the RCTs, which may have influenced the quality of the study. Finally, although no significant statistical heterogeneities were observed among the included RCTs, these studies varied with regard to the study and patient characteristics.

In conclusion, long-term treatment with DPP-4 inhibitors conferred better glycaemic control compared with SUs in patients with T2DM, which may reflect that DPP-4 inhibitors better preserve islet β-cell function than do SUs.

Conflict of interest

G. C., Y. Z. and R. Z. are employees of MSD China Holding Co., Ltd.

Author contributions

KC conceived and designed the study, collected the data, interpreted the results, wrote sections of the initial draft; DK conceived and designed the study, provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript. MY conceived and designed the study, interpreted the results, provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript. RZ and YZ conceived and designed the study, collected the data, performed analyses, interpreted the results, provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript. GC interpreted the results, provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript. YM conceived and designed the study, performed analyses, provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript. All of the authors reviewed and approved the final version of the paper.

ORCID

Yiming Mu http://orcid.org/0000-0002-3344-3540

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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