The Effect of Dipeptidyl Peptidase-4 Inhibitors on Carotid Intima-media Thickness in Patients With Type 2 Diabetes Mellitus: a Meta-analysis

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Research article

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Abstract

BACKGROUND: It is reported that dipeptidyl peptidase-4 (DPP-4) inhibitors can exert a protective effect on the cardiovascular system other than the glucose-lowering effect. However, whether DPP-4 inhibitors can delay or prevent the progression of carotid intima-media thickness (IMT), a marker for atherosclerosis, is not clear.

METHODS: An extensive literature search was performed up to December 2019.

Double-blind, randomized controlled trials that compare the effect of DPP-4 inhibitors with conventional therapy were included. The primary outcome was IMT of carotid.

RESULTS: Four studies in total involving 1141 participants were enrolled. The results indicated that DPP-4 inhibitors group showed significant decreases in IMT (- 0.022 mm, P = 0.053) when compared with control group, but it was not statistically significant. There was also a decrease in hemoglobin A1c (HbA1c) (- 0.16%, p < 0.001) in DPP-4 inhibitors groups in comparison with control groups.

CONCLUSION: Our study demonstrates DPP-4 inhibitors administrated in type 2 diabetes mellitus have no protective effects on carotid IMT compared with conventional/placebo treatment.

Introduction

Type 2 diabetes mellitus (T2DM) is a complicated disease characterized by chronic hyperglycemia with disorders of carbohydrate, protein and lipid metabolism. It mainly involves mechanisms such as β cell dysfunction, insulin resistance and impaired incretin effects. Strict glycemic control is crucial for delaying or preventing complications such as diabetic retinopathy and cardiovascular diseases.[1, 2] Up to date, there are several types of antidiabetic drugs applied in the clinic setting, including dipeptidyl peptidase-4 (DPP-4) inhibitors.

DPP-4 inhibitors emerged as a type of innovative antidiabetic medicine characterized by intermediate glucose-lowering efficacy and no additional effect on weight.[3] In addition to the hypoglycemic effect, DPP-4 inhibitors exhibited pleiotropic effects on cardiovascular system,[4] for example regulating lipid metabolism[5–7] and improving endothelial cell function.[8, 9] Among them, evidence showing that DPP-4 inhibitors may slow down the development or progression of carotid intima-media thickness (IMT) can not be ignored since IMT is universally considered to be a marker for atherosclerosis and a strong risk factor of cardiovascular adverse events.[10, 11] However, contradictions exist between studies about the effects of DPP-4 inhibitors on carotid IMT. Thus, we conducted a meta-analysis to assess this effect of DPP-4 inhibitors compared to placebo or conventional antihyperglycemic medicines.

Methods

Literature search and searching strategy

We identified potentially eligible studies through searching databases, including EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and PubMed until December 2019. Besides, in order to identify unpublished studies, we searched ClinicalTrials.gov. Search terms were used in the following: type 2 Diabetes Mellitus (T2DM); dipeptidyl peptidase-4 (DPP-4) inhibitor; Carotid Intima-Media Thickness (IMT) and Randomized controlled trial (RCT). The search strategy was presented in supplemental material.

Eligibility criteria

The inclusion criteria were: (1) Studies were RCTs;(2) Studies compared therapy of DPP4 inhibitors with placebo or other glucose-lowering drugs;(3) Study outcome comprised Carotid Intima-Media Thickness. The exclusion criteria for this study were listed as follows: (1) the duration of study was less than 12 weeks;(2) study was conducted in type 1 diabetic patients;(3) sub-studies of the original ones or different phases of the same study were ruled out.

Data extraction

Data extraction was conducted independently by two authors (XHS and LY) from included studies, including publication information (title, journal, authors, publication date), baseline characteristics of the participants (number of participants, mean age, percentage of male, duration of type 2 diabetes mellitus, body mass index [BMI], glycated hemoglobin [HbA1c], Fasting blood glucose[FBG],total cholesterol[TC], triglycerides[TG], high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL]), study arms, the duration of study and changes in IMT and HbA1c. Controversies were discussed by all authors and resolved by the consensus.

Assessment of study quality and risk of bias

Two independent reviewers (XHS and LY) assessed the quality of included studies according to the Cochrane Collaboration's tool, and any discrepancies were resolved by mutual discussion. The quality of included studies was evaluated according to Cochrane risk of bias tool in terms of selection bias, performance bias, detection bias, attrition bias, reporting bias and others. Results were considered as statistically significant if p-values < 0.05.

Statistical analysis

The weighted mean difference (WMD) and 95% confidence interval (CI) between study arms were computed for IMT and HbA1c. The heterogeneity of different studies was distributed as the $\chi 2$ statistic, and $P < 0.05$ was seen as a statistically significant threshold. The Higgins I2 statistics was the index to evaluate the percentage of variance resulting from between-study heterogeneity. A random-effects model was established to assess heterogeneity of all included studies for primary outcome. Review Manager statistical software package (version 5.3; The Nordic Cochrane Center, Copenhagen, Denmark) and STATA statistical software package (version 12.0; Stata Corp, College Station, TX) were used for statistical analyses. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results

Baseline characteristics of included studies

A total number of 108 relevant studies were retrieved from four databases: PubMed, CENTRAL, Web of Science and EMBASE. Only four articles[12–15] involving 1141 participants met all inclusion requirements and were included eventually. A search was performed in ClinicalTrials.gov, but no available clinical trial was selected in this study. The flow chart of study selection process is summarized in Fig. 1 and the baseline characteristics of analyzed studies are summarized in Table 1. Among the four studies, three studies investigated the effect of sitagliptin on the IMT while the other one explored alogliptin.

Three out of four studies compared DPP-4 inhibitors with conventional treatment (diet, exercise, and/or antidiabetic agents, other than DPP-4 inhibitors), one study compared sitagliptin with diet control (no treatment). The duration of studies varied from 48 weeks to 104 weeks. In addition, the number of patients included in each study ranged from 37 to 222.

Quality assessment of included studies

All four studies were under quality assessment according to Cochrane Handbook for systematic reviews of interventions. It was not easy to assess the reporting bias and other bias, and one study was classified to be high risk. One study did not state allocation concealment. Three studies blinded the outcome assessment appropriately, and most studies reported mean age, sex ratio, duration of diabetes, HbA1c, BMI and lipid profile at baseline. These variables of all studies were generally balanced. Overall, the risk of bias was low. The summarized risk of bias is presented in Fig. 2.

Heterogeneity and sensitivity analysis

Furthermore, we performed heterogeneity test. The results of heterogeneity test in this study showed low heterogeneity ($p = 0.178$, $I^2 = 39\%$). Sensitivity analysis was performed in the effect of DPP-4 inhibitors on IMT. As depicted by Fig. 3, one of the studies was identified as the outlier in the pooled treatment effects. After excluding the outlier study, we conducted a re-analysis of the effect, only to find the I^2 dropped from 39–0%, suggesting that this research was the major cause of study heterogeneity.

Effects on IMT

As showed in Fig. 4, there was no significant change in carotid IMT in the DPP-4 inhibitors group compared with control/conventional treatment group (WMD − 0.022 mm, 95% CI: -0.045, 0, P = 0.053; $I^2 = 39\%$, random-effects model was used). When compared with conventional treatment, the change of HbA1c in patients treated with DPP-4 inhibitors was significant (WMD − 0.16%, 95% CI: -0.169, -0.151, $P < 0.001$; Fig. 5). There was no enough data to assess the adverse event between the two groups.

Discussion

In this meta-analysis, we found that treatment with DPP-4 inhibitors resulted in no protective effects on carotid IMT compared with conventional treatments. This is contrary to many previous studies suggesting DPP-4 inhibitors attenuate the progression of carotid IMT and may potentially delay or prevent the occurrence of cardiovascular and cerebrovascular diseases. Unsurprisingly, beneficial effect of this kind of antidiabetic agents was seen on HbA1c in comparison with conventional drugs. This is consistent with what we all know.

DPP-4 inhibitors are a novel class of medicine employed in type 2 diabetes mellitus. They have been confirmed to have the potential to prevent the degradation and inactivation of GLP-1 and GIP[16–18] by inhibiting DPP-4 activity, and to increase the concentrations of GLP-1 and GIP after treatment, therefore resulting in insulin secretion and reduction of glucagon secretion. Numerous clinical studies concluded that DPP-4 inhibitors could exhibit cardiovascular protective effects in type 2 diabetic patients in addition to their antidiabetic actions. For example, vildagliptin led to significant suppression of the IL-1ß, a biomarker of inflammation involved in the initiation and progression of atherosclerosis, in patients with T2DM compared with metformin alone.[19] In another randomized clinical trial, linagliptin proved to be effective to improve microvascular function evidenced by a 34% increase in hyperemia area and a 25% increase in peak blood flow.[20] IMT is commonly accepted as a marker for atherosclerosis and cardiovascular disease. So it is reasonable to believe that DPP-4 inhibitors can also play a protective effect on carotid IMT but no conclusion yet. Indeed, accumulating studies have explored the relationship between DPP-4 inhibitors and IMT, but the results of different studies are inconsistent. No one has systematically reviewed these studies to determine the exact effect of DPP-4 inhibitors on the carotid arteries. Up to date, this is the first meta-analysis to reevaluate the effect of DPP-4 inhibitors exerted on carotid IMT.

In this study, we concluded that DPP-4 inhibitors could not attenuate the progression of carotid structural abnormality. This is inconsistent with many previous clinical studies. Nevertheless, we have to recognize that samples of studies included in this meta-analysis were all too small, making it difficult to be fully convinced. Sensitivity analysis identified one study[15] as the major cause of study heterogeneity. This is perhaps because the number of participants enrolled in this study far exceeds that of the other three studies. Therefore, the conclusion of this systematic review should be interpreted with caution. We also compared the effect of DPP-4 inhibitors on HbA1c with that of other antihyperglycemic drugs. As expected, in terms of hypoglycemic effect, DPP-4 inhibitors had advantage over conventional drugs, which was consistent with previous meta-analysis.[21–23]

We have to admit that this study had many limitations. First, there were significant differences between eligibility criteria, sample size, follow-up time, and treatment options. For example, only one study compared the efficacy of DPP-4 inhibitors and no treatment, while other studies compared DPP-4 inhibitors and conventional drugs. Although we excluded sub-analysis and extended studies and included studies with at least 48 weeks to minimize differences, we still could not guarantee the elimination of differences in other variables.

Second, ultrasound machines used to evaluate IMT and operators involved in the measurement were different, leading to possible variations in results. Also, units of some measurements between different studies have also been converted to the same units, which may contribute variations to the synthetic results as well.

Third, the limited number of patients included in this meta-analysis may be related to low credibility. So the conclusion from the comparisons between DPP-4 inhibitors and conventional agents in terms of carotid IMT should be interpreted with caution.

In summary, these results do not support that DPP-4 inhibitors provide not only glycemic control but also protective effects carotid IMT compared with conventional/placebo treatment. Of course, further studies are required to confirm our findings.

Conclusion

Our study demonstrates DPP-4 inhibitors administrated in type 2 diabetes mellitus have no protective effects on carotid IMT compared with conventional/placebo treatment.

Abbreviations

DPP-4: Dipeptidyl peptidase-4

IMT: Intima-media thickness

HbA1c: Hemoglobin A1c

T2DM: Type 2 diabetes mellitus

BMI: Body mass index

FBG: Fasting blood glucose

TC: Total cholesterol

TG: Total triglycerides

HDL: High-density lipoprotein cholesterol

LDL: Low-density lipoprotein cholesterol

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used for this meta-analysis has been contained within the manuscript.

Competing interests

There is no conflict interest to declare.

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Authors' contributions

Conception and design of the research: WYQ; Acquisition and interpretation of the data: FY, LM; Statistical analysis and writing of the manuscript: XHS, LY; Revision of the manuscript: WYQ. All authors read and approved the final manuscript.

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Conflicts of Interest

there is no conflicts of interest to declaim.

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Table

Table 1

baseline characteristics of included studies

study	study duration	treatment group	NO. of patients	mean age (year)	Men (%)	duration of DM (year)	HbA1c (%)	FBG (mmol/l)	BMI
Shinji 2014 (12)	48w	sitagliptin	37	73.7 (7.3)	86.4	/	5.77 ±0.31	5.91±0.49	25.3 ±3.9
		no treatment	39	69.0 (8.0)	84	/	5.49 ±0.29	6.01±0.64	23.8 ±3.8
Mita 2016 (13)	104w	Sitagliptin	136	63.8 ± 9.7	61	17.2 ±8.5	8.1 ±1.1	8.64 ± 2.85	25.0 ± 4.3
		Conventional	137	63.6 ± 1.0	60	17.3 ±8.7	8.0 ± 1.0	8.42 ± 2.55	25.0 ± 3.8
Mita 2015 (14)	104w	Alogliptin	161	64.4 ± 9.8	63	9 (5.0, 15.0)	7.3± 0.8	7.81 ± 1.5	24.6 ± 4.3
		Conventional	161	64.8 ± 9.1	61	8.2 (4.0, 15.0)	7.2± 0.8	7.85 ± 1.93	24.9 ± 3.7
Oyama 2016 (15)	96w	Sitagliptin	222	69.2 ± 9.3	65.8	/	6.96 ± 0.64	7.67 ± 2.31	25.3 ± 4.1
		Conventional	220	69.5 ± 9.2	68.6	/	6.96 ± 0.55	7.49 ± 2.05	24.9 ± 4.0

Table 1 Continued

study	study duration	treatment group	NO. of patients	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	IMT (mm)
Shinji 2014 (12)	48w	sitagliptin 100 mg/day	37	4.17±0.71	1.25±0.53	2.88±0.74	2.45±0.44	1.11±0.43
		con (no treatment)	39	4.29±0.80	1.21±0.68	2.96±0.84	2.41±0.49	1.02±0.44
Mita 2016 (13)	104w	Sitagliptin	136	5.02 ± 0.91	1.13 (0.83–1.55)	1.46 ± 0.37	2.85 ± 0.78	0.84 ± 0.19
		Conventional	137	4.94 ± 0.86	1.17 (090–1.72)	1.39 ± 0.38	2.78 ± 0.70	0.84 ± 0.21
Mita 2015 (14)	104w	Alogliptin	161	5.00 ± 0.77	1.19 (0.82, 1.76)	1.47± 0.38	2.89 ± 0.68	0.83 ± 0.15
		Conventional	161	5.01 ± 0.75	1.25 (090, 1.68)	1.41 ± 0.36	2.93 ± 0.64	0.83 ±0.17
Oyama 2016 (15)	96w	Sitagliptin	222	/	/	/	2.45 ± 0.67	0.829 ± 0.166
		Conventional	220	/	/	/	2.41 ± 0.73	0.835 ± 0.190

BMI: body mass index, DM: diabetes mellitus, FBG: fasting blood glucose, HbA1c: hemoglobin A1c, HDL: high-density lipoprotein cholesterol, IMT: intima-media thickness, LDL: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides.

Figures

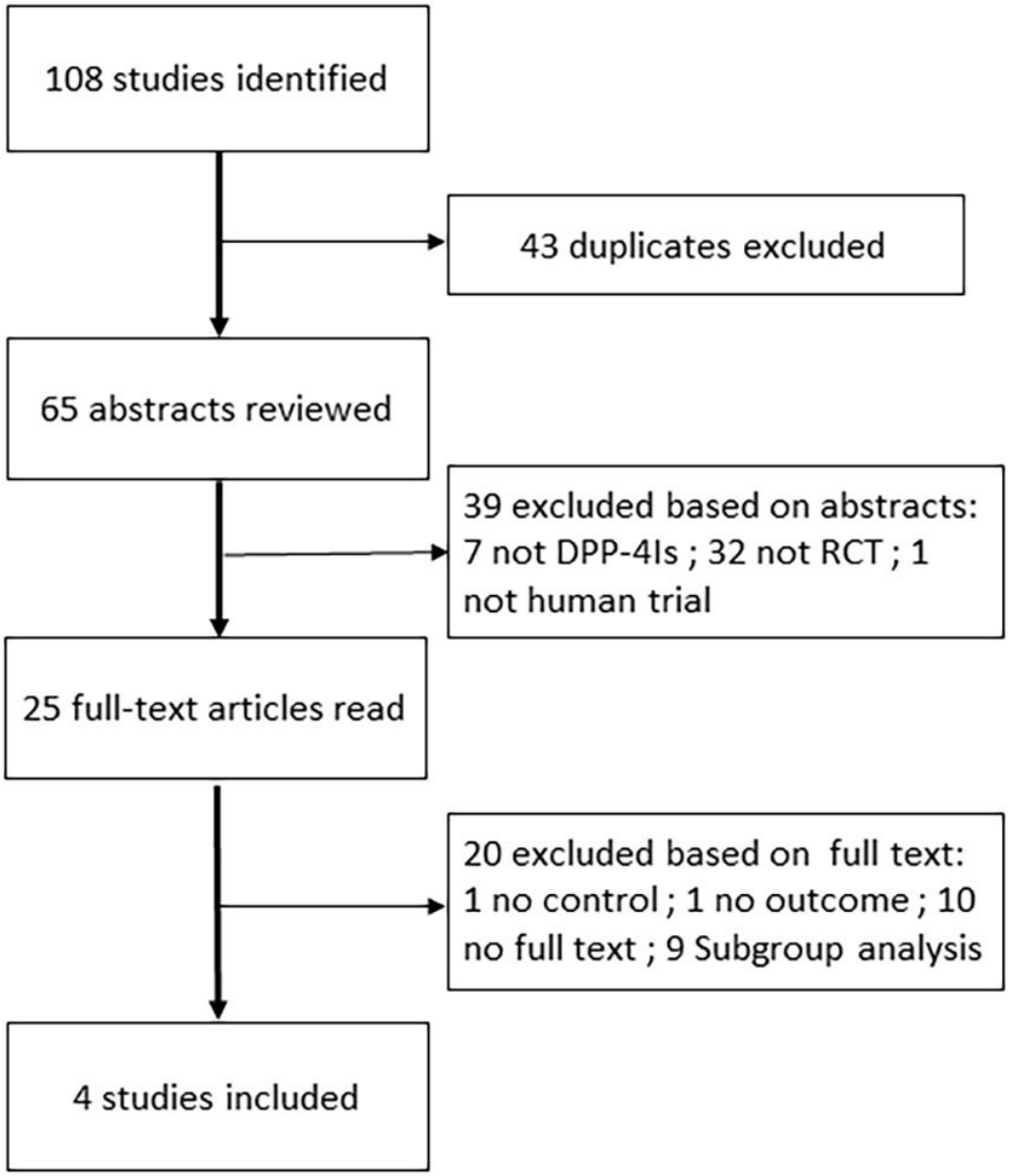

Figure 1

Flow chart of included studies. DPP-4Is, dipeptidyl peptidase-4 inhibitors

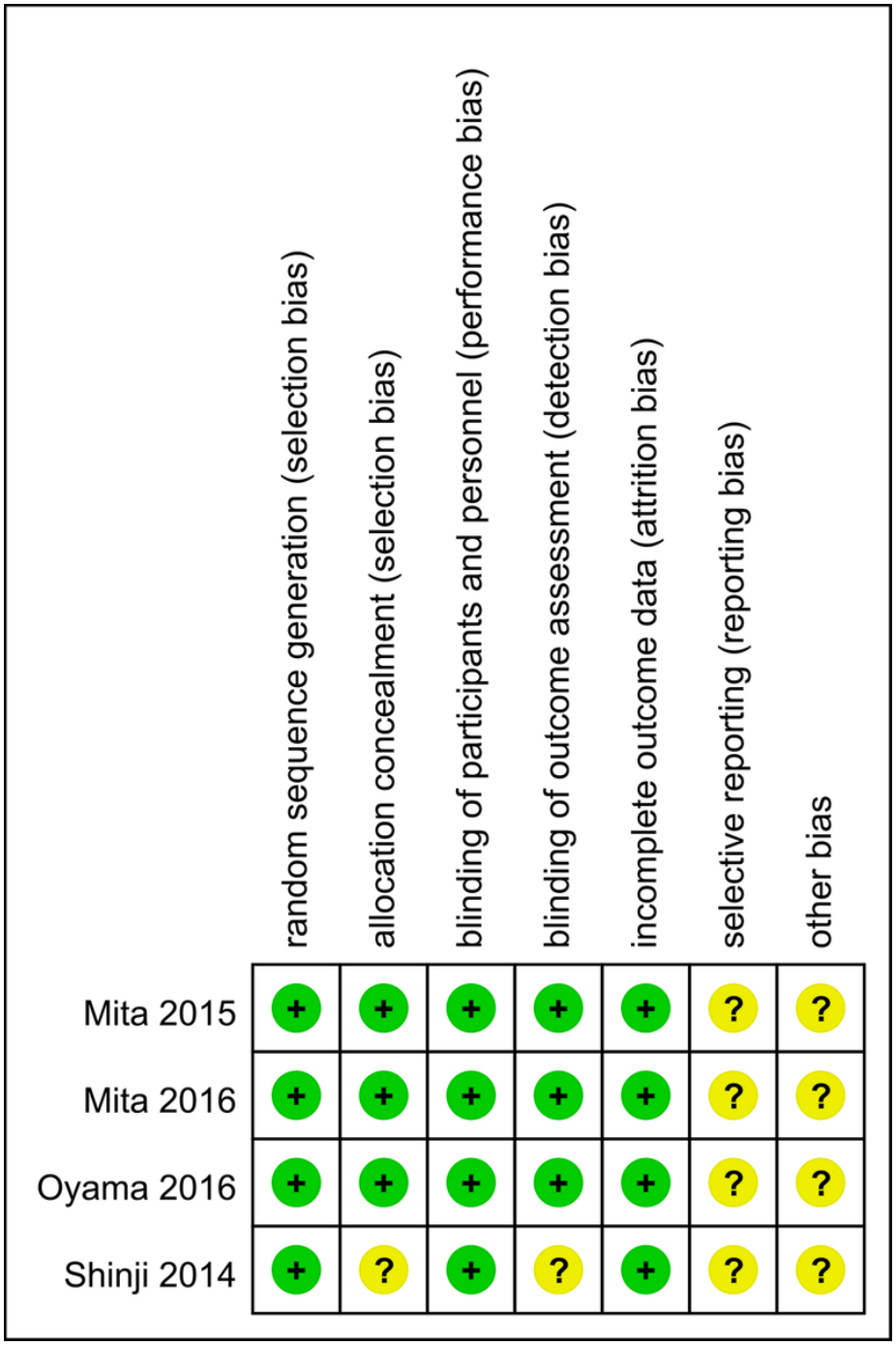

Figure 2

Risk of bias summary of the included studies

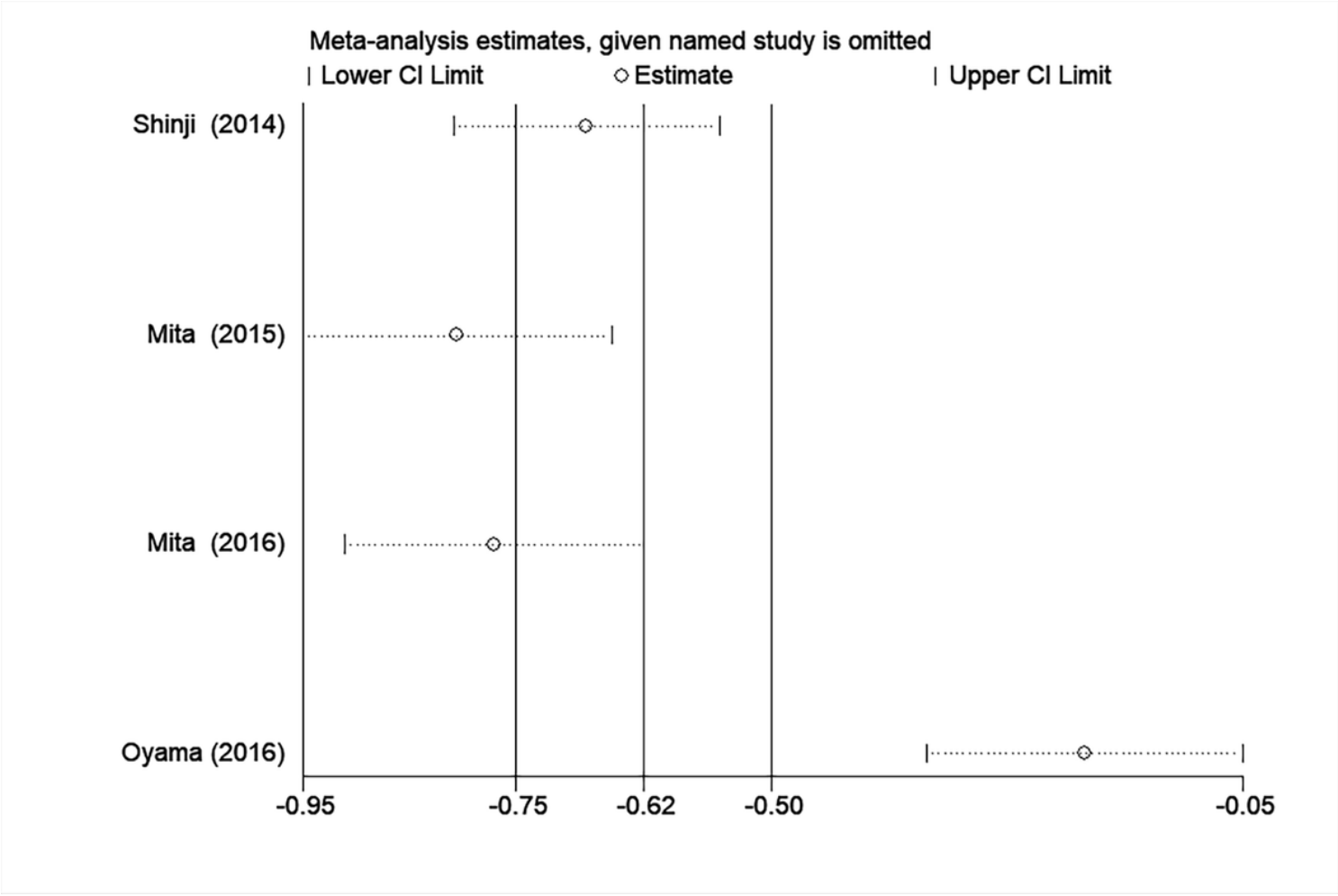

Figure 3

Sensitivity analysis for IMT

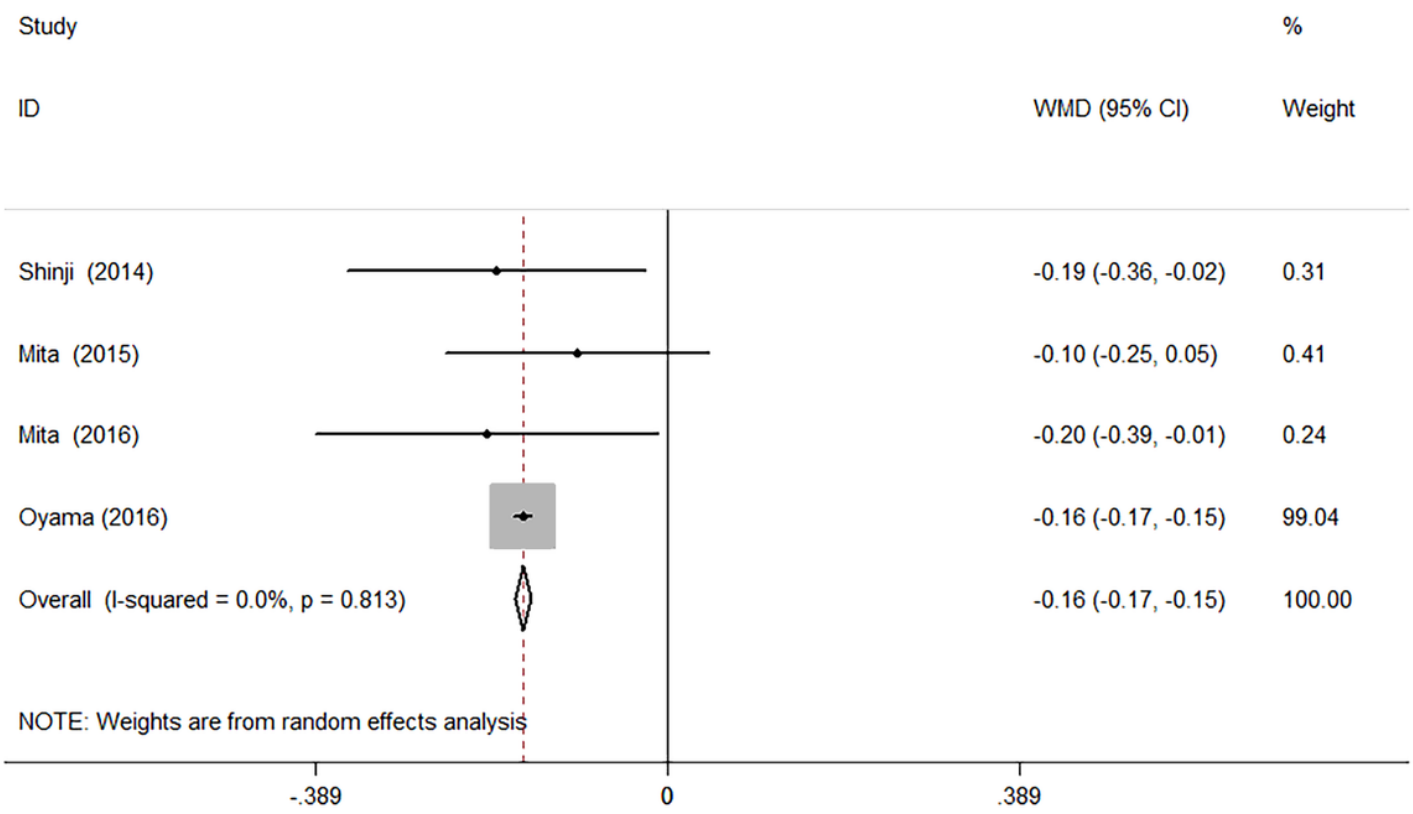

Figure 4

Change from baseline in intima-media thickness (IMT) of dipeptidyl peptidase-4 (DPP-4) inhibitor/control treatment. CI, confidence interval.

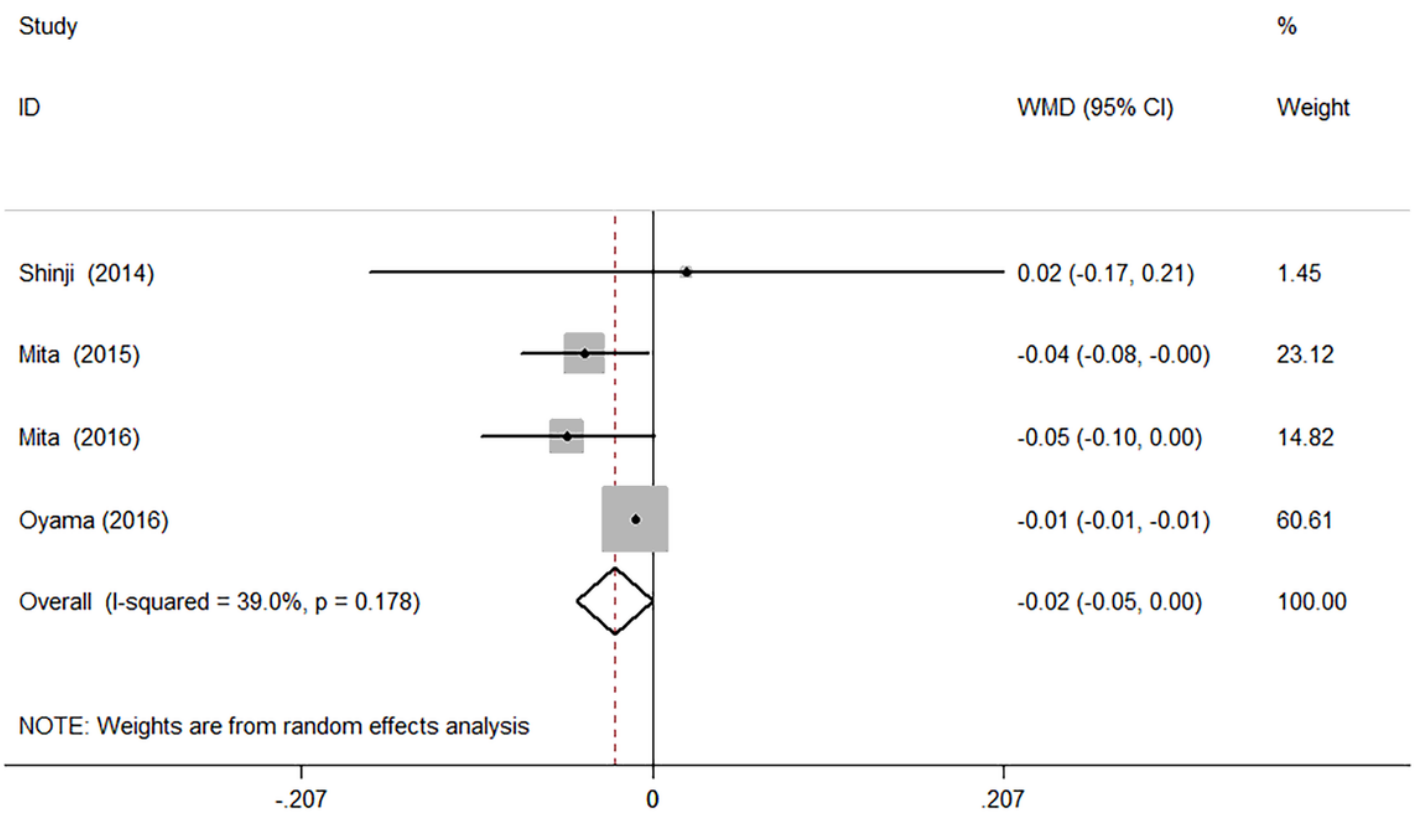

Figure 5

Change from baseline in glycated hemoglobin (HbA1c) of dipeptidyl peptidase-4 (DPP-4) inhibitor/control treatment. CI, confidence interval.

Supplementary Files

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