Effect of Dipeptidyl peptidase-4 inhibitors on the progression of atherosclerosis in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

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Abstract：

Objectives: Type 2 diabetes mellitus(T2DM) can accelerate the clinical process of atherosclerosis(AS). Dipeptidyl peptidase-4 inhibitors(DPP-4Is) have potential anti-AS effects. And, we completed a meta-analysis of the changes in carotid intima-media thickness(CIMT), flow-mediated dilation(FMD), and pulse wave velocity(PWV) of DPP-4Is to research the effect of DPP-4Is in the progression of AS in T2DM patients.

Materials and methods: We included RCTs that evaluated the impact of DPP-4Is on CIMT, FMD, and PWV compared to other treatments from PubMed, Cochrane trials, and Embase database before October 31, 2020. We selected the random-effect model and calculated the weighted mean difference(WMD) to evaluate the effect of CIMT, FMD, and PWV in T2DM patients.

Results：Through the meta-analysis, we found that DPP-4Is can significantly reduce CIMT in T2DM patients(WMD =-0.036, 95% CI:-0.055 to-0.017; p≤0.001). Based on the subgroup analysis, we found that CIMT was significantly decreased in patients with greater than 12 months of intervention and without cardiovascular diseases. Besides, we also found that DPP-4Is had a not significant efficacy on the improvement of FMD in T2DM patients(WMD=0.635, 95% CI: -0.112 to 1.383, p= 0.097). Our subgroup analysis showed that for T2DM patients who have cardiovascular diseases, DPP-4Is can significantly increase their FMD. In addition, we also found that DPP-4Is had an insignificant influence on PWV in T2DM

patients(WMD= 0.424, 95% CI: -0.198 to 1.046, p= 0.18). but SGLT2 inhibitors may reduce the PWV of T2DM patients.

Conclusions: DPP-4Is can alleviate the development of AS in T2DM patients to a certain extent by reducing CIMT. And, we believe that long-term use of DPP-4Is may be more helpful to alleviate the atherosclerotic development of T2DM without obvious cardiovascular history.

what is already known about this subject?

·Type 2 diabetes mellitus can significantly accelerate the progression of atherosclerosis.

·The role of Dipeptidyl peptidase-4 inhibitors (DPP-4Is) in the progression of atherosclerosis in patients with T2DM is still controversial.

what does this study contribute to the literature?

· DPP-4Is can alleviate the development of AS in T2DM patients to a certain extent by reducing CIMT.

·Sodium-glucose co-transporter-2 (SGLT2) inhibitors may also play a potential therapeutic role in atherosclerosis in T2DM patients.

Keyword：Dipeptidyl peptidase-4 inhibitors; Type 2 diabetes mellitus; Atherosclerosis; Carotid intima-media thickness; Flow-mediated dilation; Pulse wave velocity

1. Introduction

Atherosclerosis (AS) is a disease that is closely related to a variety of metabolic disorders. Type 2 diabetes mellitus (T2DM) can accelerate the clinical process of AS, usually lead to causing kidney, brain, and heart ischemia, thus increasing the mortality of T2DM [1,2]. Therefore, as one of the most serious complications of T2DM, AS is an important reason for the decline in the quality of life and the increased economic burden of T2DM patients [3]. The number of patients with T2DM in the world is approximately 171 million, and it is expected to at least double by 2030[4].

The clinical index of carotid intima-media thickness (CIMT) refers to the distance from the media-intima interface to the adventitia-media interface. AS is a pathological process of arterial wall thickening caused by the thickening of the

innermost layer (intima) and the middle layer [5]. Therefore, CIMT can be used as an indicator to predict early AS and to evaluate possible cardiovascular and cerebrovascular diseases [6,7]. Flow-mediated dilation (FMD) as a non-invasive technique can be highly sensitive to determine endothelial function. Its result represents the diastolic capacity of the brachial artery under chemical or mechanical stress. The decrease of FMD is directly related to endothelial dysfunction[8]. In addition, many studies have shown that endothelial dysfunction is very important for the occurrence and development of AS [9]. Pulse wave velocity (PWV) can non-invasively assess arterial stiffness [10], and the higher the PWV, the higher the risk of cardiovascular events [11]. PWV also represents the structure and function of the artery, so it is a sign of early AS [12]. Therefore, evaluation of CIMT, FMD, and PWV can help patients with T2DM improve their condition.

Dipeptidyl peptidase-4 inhibitors (DPP-4Is) are a class of drugs that lower blood sugar. Its mechanism of action is to effectively maintain the level of glucagon-like peptide-1 (GLP-1) in the body and inhibit its degradation. This can promote the secretion of insulin by the islet B cells in the body. GLP-1 analogs and DPP-4Is have also been gradually found to not only effectively lower blood sugar, but also improve the positive cardiovascular effects, including anti-AS [13,14]. According to reports, GLP-1 and its receptor agonists can effectively inhibit AS and Anti-inflammatory in rodent models of AS [15].

The effect of DPP-4Is on endothelial dysfunction [16], Arterial stiffness [11], and CIMT [17] in diabetic has been controversial. These two indicators are the key indicators to measure the progress of AS. Meta-analysis is a dependable method that can resolve differences in research. However, there is no meta-analysis on the influence of DPP-4Is on atherosclerotic progression in patients with T2DM. Therefore, we completed a meta-analysis of the changes in CIMT, FMD, and PWV of DPP-4Is to research the effectiveness of DPP-4Is in slowing the progression of AS in patients who have T2DM.

2. Materials and methods

2.1 Search strategy

The meta-analysis we completed was conducted in accordance with the PRISMA statement reporting project(Supplementary Literature 1). We searched Embase database, PubMed database, Cochrane trials database from the establishment to October 31, 2020 related documents. We use the search strategy of MeSH terms combined with free-text. The MeSH terms we used in this study are: "Dipeptidyl-Peptidase IV Inhibitors", "Diabetes Mellitus, Type 2", “Flow-mediated dilation”, “Flow-mediated vasodilation”, “Flow-mediated dilatation”, “Endothelial function”, “Pulse wave velocity”, “arterial stiffness”, and "Carotid Intima-Media Thickness"(Table 1). After that, we will import the retrieved literature into EndNote software for screening.

2.2 Study Selection

We screened the studies based on the following inclusion criteria: 1. All included studies are randomized controlled trials (RCTs); 2. The intervention group was defined as DPP-4Is plus conventional treatment or DPP-4Is alone, and the control group was defined as other treatments or placebo treatment. 3. All people included in the study are adults with T2DM (>18 years old); 4. No DPP-4Is or GLP-1 receptor agonists was used before inclusion in the study; 5. No DPP-4Is or GLP-1 receptor agonists were found in the control group; 6. In the results, each group reported CIMT, FMD, or PWV data before and after the intervention, or the change in these data; 7. All case reports, review, non-RCTs, and animal experimental studies are not included, and we do not set language restrictions on the searched documents. In addition, we also screened the references of the retrieved trials or reviews to supplement our included literature. Two researchers carefully read the literature to screen the literature and selected the qualified literature to be included in our study. In addition, we have also eliminated the differences between researchers through multi-party communication.

2.3 Data acquisition and quality assessment

Two independent researchers used a standardized data extraction table to extract

the following characteristics from the trial: publication year, first author, country of publication, number of patients, control group, follow-up time, age of admission, CIMT, FMD, or PWV mean and standard deviation (SD) or the change value of these data before and after intervention, Participant's gender, complication, and DPP-4I type. If the corresponding data is incomplete in our data extraction, we will contact the corresponding researcher to supplement the missing data. Two independent researchers used the Cochrane Collaboration Tool to evaluate the quality of RCTs, Including randomization sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other forms of bias.

2.4 Statistical analysis

We used STATA 16.0 software (STATA, Texas, USA) to complete a meta-analysis of our included studies, and we introduced the relevant changes before and after the clinical study. Since the result of each analysis is the same, we use the weighted mean difference (WMD) to analyze the summary estimate, and we use the random-effects model. By using I^2 statistics which assesses the heterogeneity of combining the results of individual studies (defined as significant when I^2>50%). In addition, to research the possible sources of the heterogeneity of DPP-4Is treatment effects, we conducted sensitivity analysis and subgroup analysis. Use funnel charts to visually assess publication deviations, and use Egger’s and Begg’s tests and the "pruning and filling" method for statistical evaluation.

2.5 Patient and Public Involvement

No patient involved.

3. Results

3.1. literature search

A total of 207 DPP-4Is studies on CIMT, FMD, or PWV in patients with T2DM were searched from the above databases. We first excluded 78 repetitive articles, and then we excluded 101 articles according to the title and abstract. Ayaori's [18] control groups were including DPP-4Is, so these studies were excluded. Overall, 27 articles

were evaluated, including 6 CIMT RCTs [19-24] (include two conference abstracts), 13 FMD RCTs [16,23,25-35] (include two conference abstracts), and 9 PWV RCTs [10,36-43] (include two conference abstracts). All the included conference abstracts and the research included in the literature do not overlap. (Figure 1A). Among them, Jun-ichi Oyama 2016 [22], Maruhashi 2016 [32], and Tomiyama 2016 [38] are the same sample research, respectively about CIMT, FMD and PWV.

3.2 Characteristics of the studies

There were 2053 subjects finished research in these studies. The population included in each study ranged from 30 to 385. The DPP-4Is used in these researches were alogliptin, vildagliptin, linagliptin, sitagliptin, and saxagliptin. These studies were followed up for 3 to 24 months. We collected relevant information from these studies (Table 2 and Table 3). The quality of studies conducted in these studies was evaluated (Figure 1B).

3.3 Results of meta-analysis

3.3.1 CIMT assessment

The meta-analysis combined data from 990 participants (control group= 540, intervention= 550). We used a random-effects model to complete a meta-analysis of the changes before and after CIMT intervention in these 6 RCTs. Through meta-analysis, we found that DPP-4Is can significantly reduce CIMT of patients (WMD= -0.036, 95% CI: -0.055 to -0.017, I^2= 96.15%, p≤0.001) (Figure 2A). Then, we stratified the study according to the duration of intervention, study population, control group measures (Figure 2B). Random-effects model shows that DPP-4Is can significantly reduce the CITM of T2DM when the intervention time is 24 months (WMD= -0.036, 95% CI: -0.055 to -0.016, I^2= 96.92%, p≤0.001). We also found that DPP-4Is can significantly reduce CIMT in patients with T2DM who were without cardiovascular diseases (WMD= -0.035, 95% CI: -0.055 to -0.015, I^2= 98.45%, p≤0.001).

3.3.2 FMD assessment

The meta-analysis combined data from 635 participants (control group= 330, intervention= 305). Through a meta-analysis of 13 RCTs, the results showed that

DPP-4Is can not significantly improve FMD in patients who have T2DM (WMD= 0.635, 95% CI: -0.112 to 1.383, I^2= 66.7%, p= 0.097) (Figure 3A). Then, we stratified the study according to the duration of intervention, study population, control group measures (Figure 3B). The random-effects model showed that DPP-4Is can significantly improve endothelial function in patients who have complicated with cardiovascular diseases (WMD= 2.487, 95% CI: 1.373 to 3.600, I^2= 32.92%, p≤0.001).

3.3.3 PWV assessment

The meta-analysis combined data from 609 participants (control group= 317, intervention= 292). Through meta-analysis, we found that compared with the control group, the effect of DPP-4Is on PWV was not significant (WMD= 0.424, 95% CI: -0.198 to 1.046, I^2= 90.24%, p= 0.18) (Figure 4A). Then, we stratified the study according to the study population and control group measures (Figure 4B). Interestingly, we found that sodium-glucose co-transporter-2 (SGLT2) inhibitors combined with metformin can significantly reduce PWV in patients with T2DM (WMD= 1.488, 95% CI: 1.364 to 1.611, I^2=0%, p≤0.001).

3.4 Publication bias analysis and sensitivity analysis

There are more than 10 studies on FMD, and we used Egger's and Begg's test to test for publication bias. According to the Egger's test, there was no publication bias in the FMD studies (Begg's test, p = 1.55; Egger's test, p = 0.22). Besides, there is no publication bias by observing the funnel chart (Figure 5A). In order to research the influence of each independent study on the size of the combined influence, we excluded each trial one by one from the combined analysis and explained their individuality. We have not observed a significant impact on the size of the combined effect in FMD and PWV studies. In the study of CIMT, we found that the heterogeneity decreased significantly after excluding Tomoya Mita 2016a [21] (WMD= -0.031, 95% CI: -0.033 to -0.029, I^2= 0%, p≤0.001) (Figure 5B).

4. Discussion

To our knowledge, our meta-analysis is the first to research the efficacy of DPP-4Is on the progression of AS in T2DM patients. Our meta-analysis evaluated the impact of DPP-4Is on their CIMT, FMD, and PWV in 2053 subjects. Our research shows that DPP-4Is can significantly decrease CIMT in patients with T2DM. In addition, according to subgroup analysis, we also found that when the intervention time was 24 months or the included population had no other comorbidities, the reduction in CIMT was more significant. At the same time, we completed a meta-analysis of 12 RCTs related to FMD, which showed that DPP-4Is did not statistically improve FMD. The subsequent subgroup analysis showed the included population was T2DM with cardiovascular diseases, DPP-4Is were significantly related to the improvement of FMD. In addition, we found that DPP-4Is has no significant effect on PWV. Interestingly, subgroup analysis showed that SGLT2 inhibitor combined with metformin may effectively reduce PWV in patients with T2DM. Therefore, DPP-4Is can effectively alleviate the development of AS in T2DM patients to a certain extent by reducing CIMT.

AS is one of the main pathological outcomes of diabetic vascular disease, which is caused by chronic inflammation and endothelial damage [44]. As an intestinal hormone, GLP-1 can promote the secretion of insulin in the body through glucose. In addition, GLP can also inhibit the secretion of glucagon in the body, thereby effectively maintaining the stability of blood sugar [45]. The level of GLP-1 in T2DM patients was lower than normal [46]. DPP-4Is are a new class of hypoglycemic drugs that can be used to treat T2DM. Such drugs can protect GLP-1 and GIP (glucose-dependent insulinotropic polypeptides) from the degradation of DPP-4 (CD26) enzymes, thus improving insulin secretion of islet beta cells stimulated by postprandial stimulation [47]. In addition to the antidiabetic effect, DPP-4Is may also have latent cardiovascular protection in patients with T2DM. Both DPP-4Is and GLP-1R agonists (GLP-1RAs) can reduce AS in animal models [48]. Inflammation has been considered as an important cause of AS and cardiovascular disease [49]. DPP-4 (CD26) is expressed on various cell membranes, including leukocytes, and mediates

pro-inflammatory signals [50]. An RCT showed that sitagliptin can reduce the expression of inflammation-related genes in vivo, reduce the concentration of IL-6 and CRP, and may potentially inhibit AS. The decrease in the expression of CD26 indicates that sitagliptin not only inhibits the synthesis of DPP-4 but also inhibits the expression of CD26 gene [51]. Studies have shown that assessing the local inflammation and oxidation of blood vessel walls, rather than serum, is helpful to comprehensively assess the "sugar-independent" anti-AS impacts of DPP-4Is [52]. The decrease in average blood glucose drift is significantly positively correlated with systemic vascular inflammation-related markers (such as IL-18 and IL-6) and oxidative stress [53]. The application of DPP-4Is to decrease blood glucose excursion may prevent the progression of AS in T2DM patients by reducing inflammatory oxidative stress [54].

Our study shows that DPP-4Is can significantly decrease CIMT in patients who have T2DM. CIMT is not only an alternative endpoint for cardiovascular events but also a good marker for early AS [55]. Researches have shown that CIMT is closely related to glycosylated hemoglobin (HbA1c) and fasting blood glucose (FPG), and there is a significant positive correlation. For every 1% increase in HbA1c, the CIMT will increase by 0.016 mm on average, and for every 10 mg/dL increase in FPG, the CIMT will increase by 0.004 mm on average [56]. It is worth noting that for every 100-micron increase in the absolute value of CIMT, the probability of stroke will increase by 13% to 18%, and the probability of myocardial infarction will increase by 10% to 15% in the future [7]. Some preclinical studies have shown that DPP-4Is exert anti-atherosclerotic effectCs by enhancing the activity of GLP-1, directly inhibiting the proliferation of smooth muscle cells and inflammatory responses of monocytes [57]. Although the definite mechanism by which DPP-4Is reduce CIMT is currently unclear, our meta-analysis showed that the influence of DPP-4Is on CIMT is clinically significant. Our results strengthen the benefits of DPP-4Is in the therapy of T2DM. At the same time, its cardioprotective and anti-AS effects are also possible. It can be attributed to its ability to reduce CIMT. The subgroup analysis showed that the

reduction of CIMT in patients who have T2DM with cardiovascular diseases was not significant. Cardiovascular trials conducted by alogliptin, saxagliptin, and sitagliptin showed that these drugs had no adverse effects in patients with high cardiovascular risk in T2DM, but they did not show any advantages compared to placebo [58]. Interestingly, although studies have shown that the saxagliptin group increases the high risk of heart failure hospitalization, the increased risk of heart failure hospitalization does not cause all-cause death or cardiovascular death [59]. Meanwhile, our subgroup analysis also found that the long-term (24 months) effect of CIMT for DPP-4Is was better than that of short-term (12 months). Therefore, we believe that the long-term use of DPP-4Is may help prevent the progression of CIMT in patients who have T2DM without obvious cardiovascular history. Through sensitivity analysis, we also determined that the Tomoya Mita 2016a study is a source of heterogeneity, which may be related to its experimental design, population type, sample size, CIMT measurement method, or the application of other drugs during the trial.

Through meta-analysis, we found that DPP-4Is had an insignificant influence on FMD in T2DM patients. As a non-invasive test, FMD has been widely used in the detection of endothelial function [27]. Endothelial dysfunction is a precursor of AS [47]. A meta-analysis by Inaba et al. showed that the combined relative risk of cardiovascular events for every 1% increase in FMD was 0.87 (95% CI: 0.83-0.91) [60]. In an animal experimental model, sitagliptin may regulate the MAPK and AMPK pathways, and then reduce the leukocyte-endothelial cell interaction and inflammation [61]. However, we found through meta-analysis that DPP-4Is does not affect on FMD. In addition, the short-term effect of DPP-4Is in improving FMD has been controversial. Because some long-term studies have shown that DPP-4Is have an anti-AS efficacy [34]. But our subgroup analysis found that long-term use of DPP-4Is (**>** 12months) can not significantly improve FMD in patients. A previous meta-analysis showed that DPP-4Is may be safe for T2DM patients in terms of

cardiovascular events [62]. In addition, sitagliptin treatment has a neutral effect on the left ventricular diastolic function of diabetic patients. Our subgroup analysis found that DPP-4Is can significantly improve FMD in T2DM patients who have cardiovascular diseases. Our meta-analysis also supports the cardiovascular safety of DPP-4Is.

Through the meta-analysis, we know that DPP-4Is have no significant effect on the PWV of T2DM patients. Overall, in the general population, PWV is an effective independent predictor of future cardiovascular events and all-cause mortality [63]. Some prospective studies have shown that in healthy subjects, arterial stiffness progresses significantly every year [64]. Interestingly, subgroup analysis shows that SGLT2 inhibitor combined with metformin can effectively reduce PWV. Studies have shown that impaired cardiac autonomic nerve function and elevated blood pressure are the main causes of abnormal PWV in patients with T2DM [65]. In addition, the use of renin-angiotensin system blockers to strictly control blood pressure, and the use of statins to control cholesterol can reduce the progression of arterial stiffness in this population [37]. A new type of hypoglycemic drug, SGLT2 inhibitor can effectively reduce blood pressure in patients who have T2DM, which is derived from its natriuretic effect [66].

Through subgroup analysis, we found that DPP-4Is have a better efficacy on reducing CIMT in T2DM patients without cardiovascular diseases. However, we also found that it can significantly improve FMD in T2DM patients who have cardiovascular diseases. In the development of AS, CIMT can reflect the injury on the anatomic level, while FMD represents endothelial dysfunction, therefore FMD changes are more sensitive than CIMT, and changes will appear earlier. However, the value of FMD is variable and is affected by multiple independent factors such as hypertension [67] and smoking [68]. Since CIMT is more specific, this indicator will be more dependable. More importantly, CIMT is more helpful in assessing the progression of cardiovascular risk over time [69]. We believe that FMD and CIMT respectively reflect different cardiovascular changes, namely functional impairment

and anatomical injury, and therefore reflect different degrees of cardiovascular risk. Therefore, DPP-4Is may be more helpful to alleviate the progression of AS in T2DM patients with no obvious cardiovascular history.

Strengths and limitations of this study:

1. All of the researches we included were RCTs.
2. In our meta-analysis, no DPP-4Is were in the control group, and we excluded studies that took DPP-4Is before inclusion.
3. Due to the potential positive effects of SGLT2 inhibitors on PWV, our meta-analysis may have certain guiding significance for subsequent research.
4. limitations include this meta-analysis included relatively few studies. Therefore, it is necessary to carry out more extensive and more standardized clinical studies.

5. Conclusion

Our study showed that DPP-4Is can alleviate the progression of AS in T2DM patients to a certain extent by reducing CIMT. Then, combined with our subgroup analysis and comparison of CIMT and FMD, we believe that long-term use of DPP-4Is may be more helpful to alleviate the atherosclerotic progression of T2DM without obvious cardiovascular history. Although our meta-analysis shows that DPP-4Is can alleviate the progression of AS in T2DM patients, Large-scale and standardized prospective researches are still needed to ensure the effectiveness of DPP-4Is in the primary prevention of cardiovascular disease in T2DM patients.

Supporting information

S1 File. PRISMA checklist.

Acknowledgments

Technical Support: Kun Zhao

Author Contributions

YTT participated in the research design. LWW, LRX, LYF conducted a literature search, screening data extraction. SHS analyzed the data, and did a statistical analysis, and wrote a manuscript. PM and LRX participated in the correction of the manuscript. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript.

Competing financial interests: The authors declare no competing financial interests.

Project fund: This project is funded by the National Natural Science Foundation of China (no.81473631). The sponsors are not involved in design, execution, or writing the study.

Data Availablity Statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ira Approval: Not required for this study.

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Legend:

Figure 1: (A): Flow diagram of study selection; (B) Included in randomized controlled experiment literature quality evaluation (B1): CIMT; (B2): FMD; (B3): PWV. Note: Red means high risk, green means low risk, yellow means unclear

(1): Random sequence generation (selection bias)

(2): Allocation concealment (selection bias)

(3): Blinding of participants and personnel (performance bias)

(4): Blinding of outcome assessment (detection bias)

(5): Incomplete outcome data (attrition bias)

(6): Selective reporting (reporting bias)

(7): Other bias

Figure 2: (A):Forest plot to study the effect of DPP-4 inhibitor on carotid intima-media thickness (CIMT); (B): Subgroup analysis of the effect of DPP-4 inhibitor on carotid intima-media thickness (CIMT)

Figure 3: (A):Forest plot to study the effect of DPP-4 inhibitor on Flow-mediated dilation (FMD); (B): Subgroup analysis of the effectof DPP-4 inhibitor on Flow-mediated dilation (FMD)

Figure 4: (A):Forest plot to study the effect of DPP-4 inhibitor on Flow-mediated dilation (PWV); (B): Subgroup analysis of the effect of DPP-4 inhibitor on Flow-mediated dilation (PWV)

Figure 5: (A): Funnel plot of weighted mean difference (WMD) in FMD related studies; (B1): Sensitivity analysis (CIMT); (B2): Sensitivity analysis (FMD); (B3): Sensitivity analysis (PWV)

Table 1: PubMed Search terms

Table 2: (A): Basic information of included studies (CIMT); (B): Basic information of included studies (FMD); (C): Basic information of included studies (PWV)

Table 3: (A): Included outcome indicators (CIMT); (B): Included outcome indicators (FMD); (C): Included outcome indicators (PWV)