The effect of Thiazolidinediones on the vascular endothelium and plaque in diabetic patients with coronary atherosclerosis：a meta-analysis

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Article

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Abstract

Rosiglitazone (Avandia) and Pioglitazone (Actos) belong to the class of thiazolidinedione drugs that act by increasing insulin sensitivity and are widely used for treating diabetic patients with insulin resistance. Thiazolidinediones (TZDs) exhibit anti-inflammatory and antioxidant properties and inhibit endothelial cell inflammation and dysfunction, and then play a role in inhibiting plaque formation and coronary atherosclerosis. But the results of evidence-based medicine suggest that thiazolinedione may increase the risk of myocardial infarction. To explore the dispute in depth, the meta-analysis aimed to evaluate the changes in vascular endothelial and plaque-related indicators following treatment with thiazolidinediones on diabetic patients with coronary atherosclerosis.According to our meta-analysis, Thiazolinediones showed a protective effect on the vascular endothelium and an inhibiting effect on plaque progression in patients with diabetes and coronary atherosclerosis and these effects may not depend on related targets or pathways such as inflammation and lipid regulation. Due to the poor quality of the evidence, more and higher-quality studies are needed to further improve the above conclusions.

Introduction

Globally, 537 million adults (20–79 years) are living with diabetes. This number is predicted to rise to 643 million by 2030 and 784 million by 2045. Diabetes mellitus has been approved to be associated with increased risk of cardiovascular disease. Many studies have shown that people with diabetes are 2–4 times more likely than the general population to develop cardiovascular disease and have an increased mortality risk.There are increasing numbers of patients who suffer from diabetes and comorbid cardiovascular disease. In general, simple diabetes and diabetes combined with cardiovascular disease have different treatment purposes and specific principles. To find a drug with both hypoglycemic action and cardiovascular protecting effect is very necessary.

Rosiglitazone and pioglitazone belong to the class of thiazolidinedione drugs that act by increasing insulin sensitivity and are widely used for treating patients with type 2 diabetes mellitus (T2DM). Thiazolidinediones (TZDs) exhibit anti-inflammatory and antioxidant properties and inhibit endothelial inflammation and dysfunction, which are thought to be the major causes of coronary atherosclerosis .Accordingly, TZD is believed to have a role of preventing coronary atherosclerotic heart disease. But currently, there has been controversy over thiazolinediones in the cardiovascular field. A meta-analysis in May 2007 showed for the first time that rosiglitazone increased the risk of 43% myocardial infarction, which showed that such types of drugs may have cardiovascular adverse effects. Subsequently, a series of evidence-based medical evidence was published that the increased risk of heart failure is relatively cle, r,but they failed to reach consistent conclusions on the myocardial infarction risk of thiazolidinediones. Recently, a meta-analysis with a sample size of 21156 concluded the effects of rosiglitazone treatment on cardiovascular risk and mortality. The results suggest that rosiglitazone is associated with an increased cardiovascular risk, especially for heart failure events. The odds ratios for myocardial infarction were 1.17, which suggests 17% risk increase of myocardial infarction after rosiglitazone intervention. The authors were cautious about this because of the small confidence intervals and large diversity between

different analysis methods. Hence, the relationship between rosiglitazone and myocardial infarction was still not clarified.

Endothelium, whose dysfunction is implicated in a number of pathophysiologic processes, including atheromatous plaque formation and coronary artery pathological changes, is considered to be an important target for thiazolidinediones intervention in coronary atherosclerosis. Our meta-analysis was designed to assess changes in vascular endothelial and plaque-related indices after rosiglitazone or pioglitazone treatment in patients with diabetes combined with coronary atherosclerosis, and to explore potential targets for the protective effects of thiazolidinediones in myocardial infarction.

Results

Search results

As shown in Fig. 1, a total of 117 studies initially were identified through different database searching. After the removal of duplication, additional screening, and analysis of the titles,abstracts and or full-texts for each of the articles, twenty-eight articles were included as eligible for this study. For articles where the full text is available,we read the full text carefully, 20 articles were excluded because they are not RCT single-handed intervention or we can’t find the full text. Finally, eight studies were included in the qualitative and quantitative review and meta-analysis inour study.

Characteristics of included studies

The main characteristics of participants and interventions are presented in Table 1. There were 451 participants enrolled in the 8 studies.

Table 1
The literature feature table was included

study	Age / year		Sample size		intervention group	Control group	duration
	I	C	I	C			
Marjorie Bastien2019	63.3 ± 7.4	64.8 ± 7.0	53	51	Rosiglitazone 8mg / d	Placebo treatment	12m
Olivier 2010	64.2 ± 7.3	65.1 ± 6.9	98	95	Rosiglitazone 8mg / d	Placebo treatment	12m
C.M.Ahn2010			47	47	pioglitazone	Placebo treatment	8m
Sung Hye You2010	59.4 ± 6.4	62.0 ± 7.4	19	18	pioglitazone	Placebo + aspirin 100 mg/d and clopidogrel 75 mg / d	8m
Hideki Kitahara 2011	66.4 ± 7.9	66.8 ± 9.6	25	25	pioglitazone	Placebo + aspirin 100 mg/d and clopidogrel 75 mg / d	9m
S. Desch 2010	61.3 ± 7.1	62.3 ± 6.5	16	12	Rosiglitazone	Placebo treatment	6m
HARALD SOURIJ 2006	NA	NA	21	21	pioglitazone	Placebo treatment	3m
J YU 2010	63.9 ± 2.2	63.3 ± 2.2	28	28	Rosiglitazone	Basic treatment	3m

Risk of bias

All eight randomized controlled trials mentioned randomization and blindness methods,We evaluate the credibility of the information provided by the articles: 1 grouped by randomized digital table; 1 literature mentioned single blindness, with the possibility of breaking blindness; the rest 6 mentioned blindness to researchers, subjects, and data analysts; insufficient data in the literature to indicate follow-up bias and reporting bias, no missing data and pre-reported outcomes have been reported. The results are shown in Fig. 2.

Effect of the TZD on the vessel volume(mm^3/mm)

There were 3 studies included in the meta-analysis to evaluate the overall effect of TZDs on vessel volume. We found a very few level of heterogeneity for vessel volume among the existing studies (I^2 = 0%, P = 0.40) (Fig. 3).Based on the fixed-effects model of meta-analysis, lower levels of vessel volume were

observed in the intervention group compared to the control subjects. (MD 95% CI: -1.28 -2.51, -0.05, z = 2.04, P = 0.04).

Effect of the TZD on the lumen volume(mm^3/mm)

There were 3 studies included in the meta-analysis to evaluate the overall effect of TZDs on lumen volume. We found a low level of heterogeneity for lumen volume among the existing studies (I^2 = 44%, P = 0.17) (Fig. 4). Based on the Fixed-effects model of meta-analysis the difference between the intervention group and the control group was not statistically significant. (MD 95% CI:0.47 − 0.17, 1.10, z = 1.44, P = 0.15).

Effect of the TZD on the plaque volume(mm^3/mm)

There were 4 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on plaque volume. We found a very few level of heterogeneity for plaque volume among the existing studies (I^2 = 0%, P = 0.61) (Fig. 5).Based on the Fixed-effects model of meta-analysis, significantly lower levels of plaque volume were observed in the Intervention group compared to the control subjects (MD 95% CI:-1.32 -1.93, -0.71, z = 4.23, P < 0.0001).

Effect of the TZD on the Adiponectin(μg/l)

There were 4 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on Adiponectin. We found a severe level of heterogeneity for plaque volume among the existing studies (I^2 = 91%, P < 0.0001) (Fig. 6).Based on the random-effects model of meta-analysis, significantly higher levels of Adiponectin were observed in the Intervention group compared to the control subjects. (MD 95% CI:5.731.31, 10.15, z = 2.54, P = 0.01).

Effect of the TZD on the hs-CRP(mg/L)

There were 4 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on hs-CRP. We found a severe level of heterogeneity for hs-CRP among the existing studies (I^2 = 79%, P = 0.003) (Fig. 7).Based on the random-effects model of meta-analysis,the difference was not statistically significant. (MD 95% CI:-0.24-0.63, 0.15, z = 1.21, P = 0.23).(See Fig. 7) For sensitivity analysis, excluding the study "Sung Hye You2010", the group heterogeneity was reduced(P = 0.36, I^2= 3%), and the fixed-effect model Meta-analysis showed: MD 95% CI:-0.51-0.62, -0.41,Z = 9.50 (P < 0.00001),lower levels of hs-CRP were observed in the Intervention group compared to the control subjects.That is, the result was unstable.

Effect of the TZD on the Interleukin-6(ng/L)

There were 2 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on Interleukin-6. We found a severe level of heterogeneity for Interleukin-6 among the existing studies (I^2 = 78%, P = 0.03) (Fig. 8).Based on the random-effects model of meta-analysis, the difference was not statistically significant. (MD 95% CI:-0.20-0.78, 0.37, z = 0.69, P = 0.49).

Effect of the TZD on the glycerin trilaurate(mmol/L)

There were 5 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on glycerin trilaurate. We found a middle level of heterogeneity for glycerin trilaurate among the existing studies (I^2 = 74%, P = 0.004) (Fig. 9).Based on the random-effects model of meta-analysis, the difference was not statistically significant (MD 95% CI:0.21 − 0.13, 0.55, z = 1.20, P = 0.23). For sensitivity analysis, excluding the study "HARALD SOURIJ 2006", the group heterogeneity was reduced(P = 0.51, I^2= 0%), and the fixed-effect model Meta-analysis showed: MD 95%CI:0.04–0.04,0.11,Z = 0.94(P = 0.35),higher levels of glycerin trilaurate were observed in the Intervention group compared to the control subjects.However, The difference remained not statistically significant,indicating that the result was unstable.

Effect of the TZD on the total cholesterol(mmol/L)

There were 5 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on cholesterol total. We found a severe level of heterogeneity for cholesterol total among the existing studies (I^2 = 83%, P = 0.0001) (Fig. 10).Based on the random-effects model of meta-analysis, the difference was not statistically significant (MD 95% CI:0.07–0.16, 0.31, z = 0.62, P = 0.54). For sensitivity analysis, excluding the study "J YU 2010", the group heterogeneity was reduced (P = 0.75), I^2= 0%), and the fixed-effect model Meta-analysis showed: MD 95% CI:0.16 0.03, 0.29,Z = 2.34 (P = 0.02), higher levels of cholesterol total were observed in the Intervention group compared to the control subjects,The differences were statistically significant, as described in summary,the result was unstable.

Effect of the TZD on the LDL-C(mmol/L)

There were 6 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on low density lipoprotein cholesterol. We found a very few level of heterogeneity for low density lipoprotein cholesterol among the existing studies (I^2 = 0%, P = 0.47) (Fig. 11).Based on the Fixed-effects model of meta-analysis, the difference was not statistically significant. (MD 95% CI:-0.02 -0.07, 0.03, z = 0.90, P = 0.37).

Effect of the TZD on the HDL-C(mmol/L)

There were 6 studies to be included in the meta-analysis to evaluate the overall effect of TZDs on high density lipoprotein cholesterol. We found a low level of heterogeneity for high density lipoprotein cholesterol among the existing studies (I^2 = 30%, P = 0.21) (Fig. 12).Based on the Fixed-effects model of meta-analysis, the difference was not statistically significant (MD 95% CI:0.02 − 0.01, 0.05, z = 1.10, P = 0.27).

Discussion

Among the various types of medicine used in diabetes patients, TZD was explored to have an inhibition effect on cardiovascular disease by regulatting blood lipid levels, serum adiponectin levels, and

inflammation[7]. But there are different conclusions to date. According to a report, Glitazones, a TZD, can reduce a range of cardiovascular risk factors, such as lipid unbalance, endothelial dysfunction, inflammatory markers, and atherosclerosis.Furthermore, a randomized controlled trial with a large sample also confirmed TZDs anti-atherosclerotic effect. This inconsistence may be due to different study populations and different testing methods. To demonstrate the role of such agents in the treatment of diabetes combined with atherosclerosis, we performed this meta-analysis.

Based on our meta-analysis, in diabetic patients with coronary atherosclerosis, TZD treating resulted in an overall improvement on vessel volume and inhibition on plaque volume. The results indicated that thiazolinediones could protect the endothelium and reduce plaques. An essential function of the endothelium is to respond to physiological stimuli and produce transient vasodilators, including nitric oxide, bradykinin, prostacyclin, and endothelial-dependent hyperpolarization factor (EDhf).The hyperglycemic state activates the endothelium and promotes foam macrophage formation. Those changes promote intimal thickening and promote endothelial dysfunction, then lead to formation of Plaque and atherosclerosis. TZD treatment could attenuate atherosclerosis lesions partially through improving endothelial function, just as described in article by Frank et al.

Diabetes is a major risk factor for coronary heart disease, and the mortality of coronary heart disease is higher in patients with diabetes than subjects without diabetes. Coronary heart disease is primarily caused by atherosclerosis of coronary arteries, which has been recognized as an inflammatory disease of the vascular wall. Among the diabetic patients with coronary atherosclerosis, the coronary artery lesions had a wide range and a severe extent. The mechanisms may be related to disordered glucose metabolism, disordered lipid metabolism, inflammatory response, endothelial injury etc[7].

The development of inflammation and dyslipidemia are involved in the formation of coronary atherosclerotic lesions. Inflammation is considered a major driver of atherogenesis and vulnerable development of atherosclerotic plaque, related to the retention and modification of lipoproteins, High-sensitive C-reactive protein (hs-CRP) is a sensitive marker of progressive systemic inflammation. In this stu, y,meta-analysis showed that serum adiponectin levels were elevated in the Thiazolidinediones intervention group. It has been proved that TZD ativated the peroxisome proliferator-activated receptor isoforms (PPARγ), which alters the transcription of several genes involved in glucose and lipid metabolism, including lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid-binding protein, fatty acyl-coenzyme A synthase, etc. Adiponectin is a protein secreted by adipocytes, and clinical and experimental observations suggest that low adiponectin plasma levels contribute to improved insulin resistance in obese or overweight patients, at the same time, low adiponectin expression is the cause of diabetic endothelial dysfunction. For indicators of big heterogeneity, we explored the source of the heterogeneity and removed it to test the stability of the results. It showed that lower levels of hs-CRP and higher levels of total cholesterol were observed in the intervention group compared to the control subjects, but they are not entirely reliable. TZD has been reported to have effect on lipid metabolism. In our study, we found that TZD had effect on the vessel, plaque and Adiponectin, although these inflammation and

blood lipids indicators showed a better trend, due to the poor sample,we cannot reach a persuasive conclusion accordingly.

Unexpectedly, the lumen volume was not made statistically significant, and we speculate that such results derive from differences between the measured equipment and the different technicians. Some of the commonly used indicators of blood lipids and inflammation, such as Interleukin-6, LDL-C, and HDL-C didn't get the statistical differences. We speculate that this is related to the quantity and quality of the literature.

Our results suggest that thiazolinediones can improve vascular endothelial and plaque-related indices in diabetic patients with atherosclerosis,and will raise the levels of Adiponectin In addition, our study showed such drugs do not affect excessive inflammatory indicators and blood lipid indicators such as interleukin and triglycerides, indicating that the above effects of thiazolinediones maybe not depend on the improvement of inflammation and blood lipids.

A recent article on the relationship between diabetes and cardiovascular disease reported on sodium glucose cotransporter 2 inhibitors and endothelin receptor antagonists, glucagon-like peptide 1 agonists, the impact of isohypoglycemic drugs on cardiovascular aspects, to ensure the optimal treatment, and preventing adverse events and unnecessary multi-drug combination provides new ideas, we believe that research should be strengthened in relevant areas.

By reviewing our study, we identified some limitations in our paper: low levels of the literature included; high heterogeneity between studies; rough integration of rosiglitazone with pioglitazone creates greater bias. We look forward to the addition of more high-quality research in this field.If the sample size is large enough,our conclusion that the effect of thiazolidinedione in improving the vascular endothelium and plaque in diabetic atherosclerosis does not depend on the improvement of inflammation and lipid profile may be more reasonable and perfect.

Methods

This meta-analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, with our protocol registered in PROPERO as CRD42021231663.

Literature search strategy

To find relevant peer-reviewed studies regarding Thiazolidinediones and Endothelium in diabetic patients with coronary atherosclerosis, different electronic databases including PubMed/Medline, EMBASE, Web of Science, and Cochrane Library were used.The search terms included"Coronary Artery Disease","Endothelium","Thiazolidinediones","Glitazones","Rosiglitazone", etc.The combinations of different search terms were used for identifying the relevant articles, and the search strategies were customized to suit each database. (see Additional file 1: Table S1).

Criteria for inclusion and exclusion

Inclusion criteria for this study were the following: (a) the study must be a randomized controlled trial design; (b) it should be published in a peer-reviewed journal in the English language; (c) studies should have clear diagnostic criteria about diabetic patients with coronary atherosclerosis; (type 2 diabetes according to the diagnostic criteria of T2DM published in the American Diabetes Association, and coronary heart disease or vascular stent surgery suggesting coronary atherosclerosis) (d) reported studies should be available in full text (not editorial,commentary,or abstract for conferences). Studies were excluded if (a) they were published in other languages than English and contained only qualitative data; (b) the intervention and control groups mixed up patients with other diseases; (c) the combination of thiazolidinediones was present in the intervention group.

Data extraction and management

Two authors (Cheng-Yuan Xue. and Meng-Qi Zhou) reviewed the titles, abstracts, and/or full-texts for each of the articles identified by the literature search after removal of duplicates, aiming to determine the eligibility for this meta-analysis. During the study selection process, discrepancies were resolved by discussion with a third author (Qi-Yan Zheng). All authors independently performed data extraction using standard extraction spreadsheets from the selected articles based on the inclusion criteria and enlisted in a table. The following items were extracted from each study: author's name (first author), year of publication, country, groups, gender distribution, mean age (years), number of participants (male vs female), vessel volume, lumen volume, plaque volume, neointima volume, flow-mediated dilatation, Adiponectin, endothelin, NO, NOS, hs-CRP, Interleukin-6, TNF-α, Triglycerides, Total cholesterol, Low density lipoprotein cholesterol, High density lipoprotein cholesterol. After the extraction of the data, the authors cross-checked the data tables and resolved any conflicts and inconsistencies during the data extraction process through discussion with each other.

Quality assessment

The quality assessment of all included studies was conducted by using the Cochrane Collaboration “Risk of Bias”tool. We expand our analysis through the following six items: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.Each entry was also classified into three levels of bias risk: "high risk", "low risk" and "uncertain risk". The two evaluators evaluated the literature quality respectively, and the differences were determined by a third party.

Statistical analysis

We used a statistical software named Review Manager V5.4.1 (Cochrane Collaboration, Copenhagen, Denmark) for the meta-analysis. The random-effect model and forest plots were adopted as the statistical method, which seems to provide more conservative results than a fixed-effects model.

We calculated the mean difference (MD) with a corresponding 95% confidence interval (CI) for each parameter using the random-effects model. The existence of heterogeneity among studies was evaluated

using I^2 and its resultant P-value using chi-squared tests. I^2 values of 0–25%, 25–50%, and 50–75% correspondence the heterogeneity as low, medium, and high heterogeneity, respectively. A P-value < 0.05 was considered a statistically significant difference between groups.

Published bias

The number of studies on the same outcome measure was too small,and publication bias was tested without funnel plots.

Declarations

Author Contributions

All authors contributed to developing the study concept and designing the study. Data collection was performed mainly by C.Y.X.,with assistance from M.Q.Z.. Q.Y.Z. performed the data analysis and interpretation. C.Y.X. and L.X.L. drafted the paper, then W.J.L. provided critical revisions. All authors approved the final version of the paper for submission.

Competing interests

The authors declare no competing interests.

Data availability declaration

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Figures

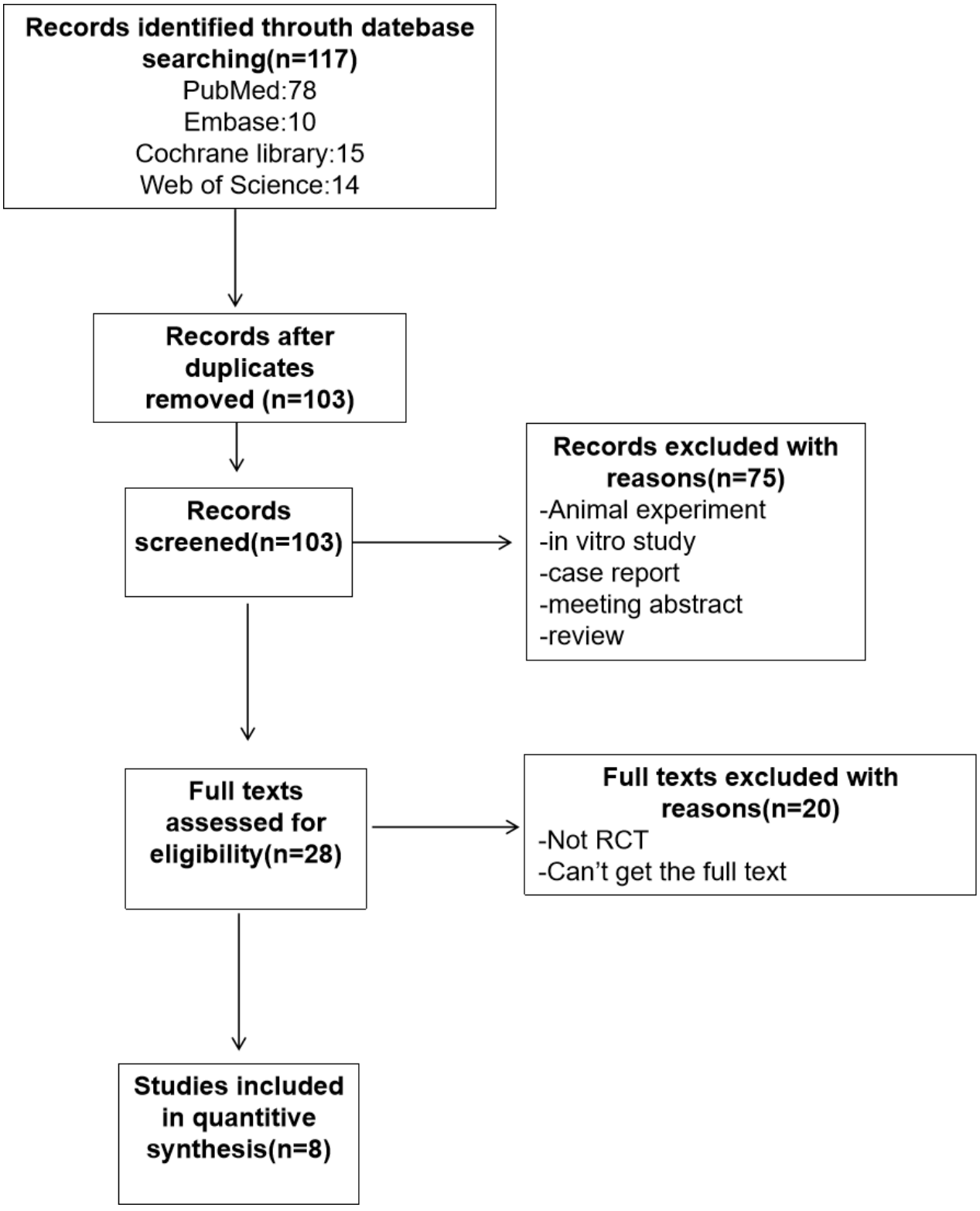

Figure 1

Flow diagram of literature search and study selection

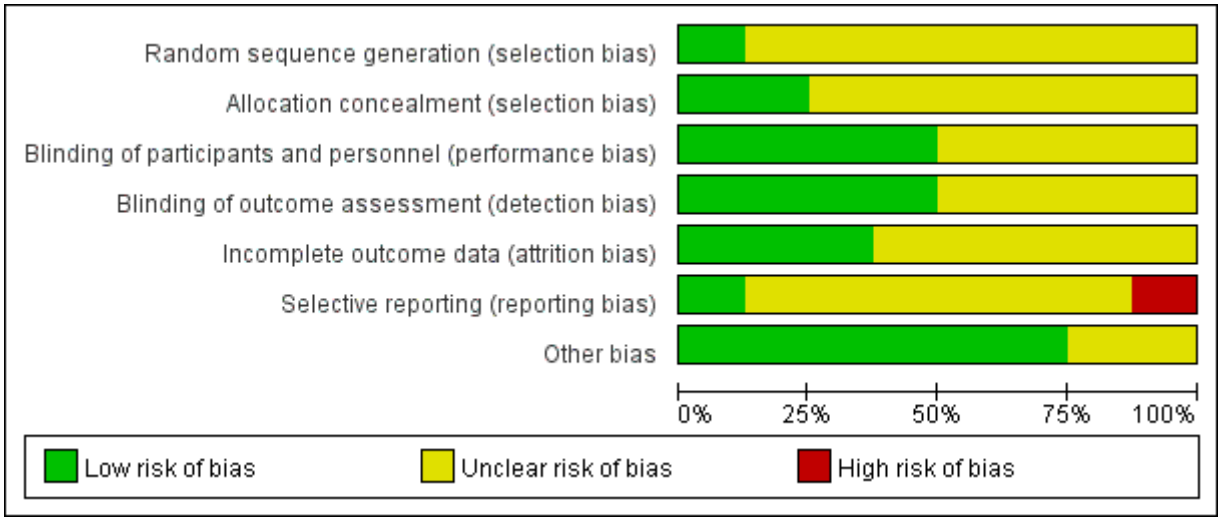

Figure 2

Schematic representation of the risk of bias

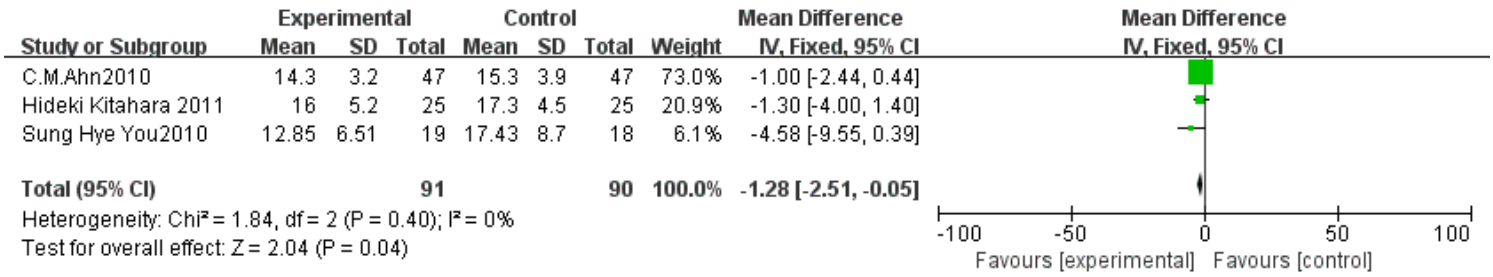

Figure 3

Effect of the TZD on the vessel volume.vessel volume is an important indicator of vascular endothelial function and plaque.

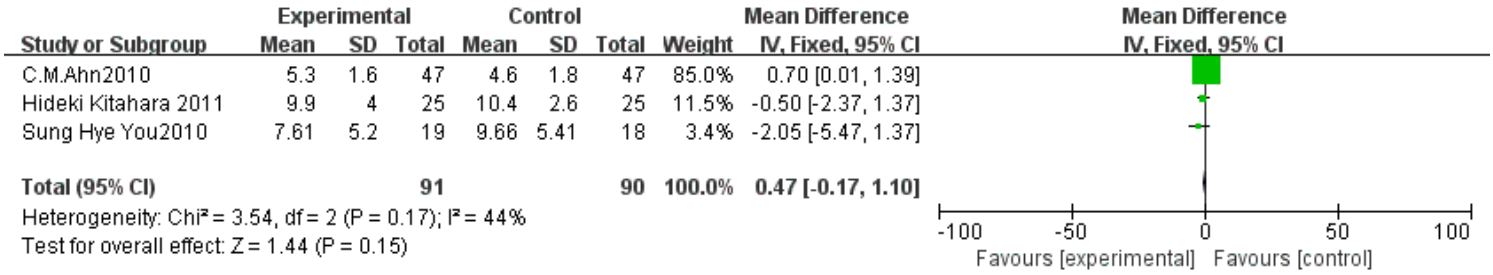

Figure 4

Effect of the TZD on the lumen volume. lumen volume is an important indicator of vascular endothelial function and plaque.

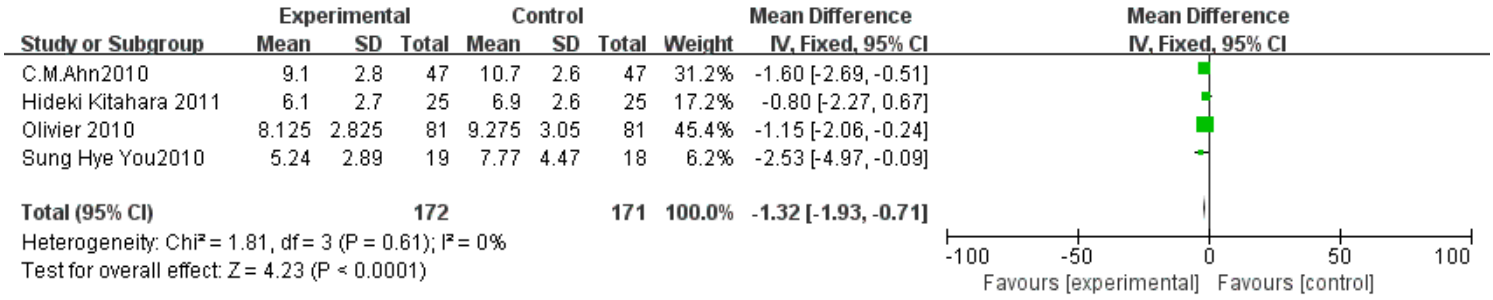

Figure 5

Effect of the TZD on the plaque volume.lumen volume is a direct indicator of plaque vascular and endothelial function.This data is the difference between the first two data, and part of the literature only report this result without mentioning the original data.

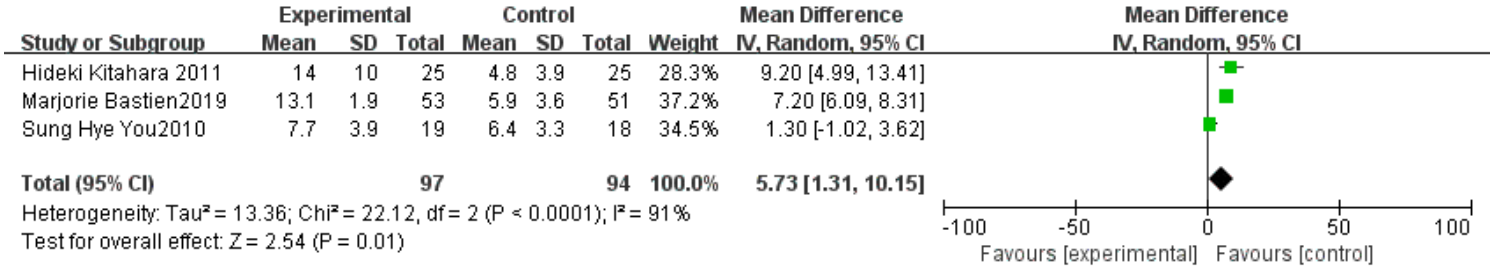

Figure 6

Effect of the TZD on the Adiponectin（APN）.Adiponectin levels can predict the progression of type II diabetes and coronary heart disease, and exhibit anti-diabetic, anti-atherogenic, and inflammatory potential.

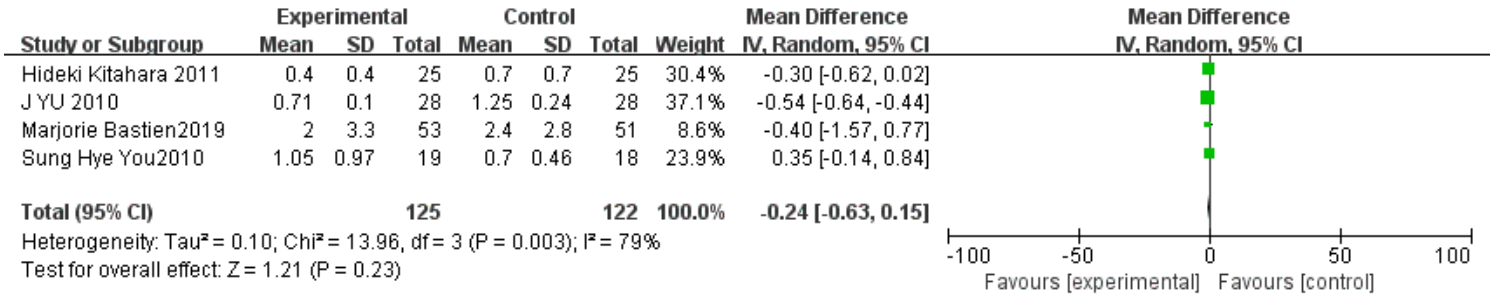

Figure 7

Effect of the TZD on the hs-CRP. The hs-CRP is a sensitivity indicator reflecting the degree of inflammation in the body, and is believed to be closely related to diabetes mellitus and coronary atherosclerosis.

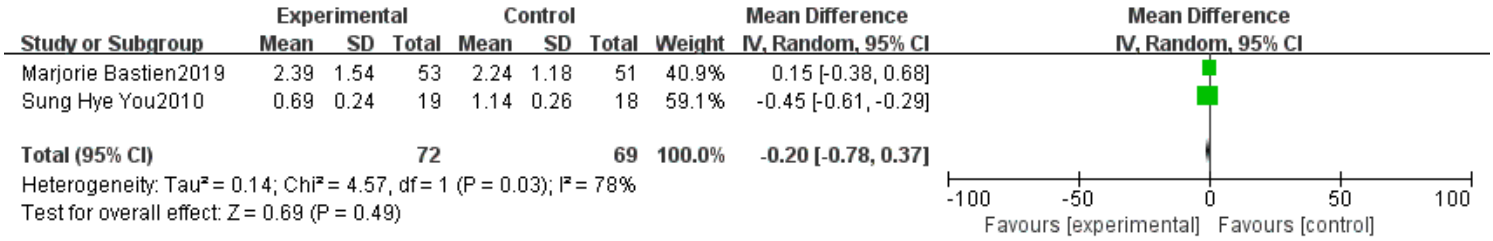

Figure 8

Effect of the TZD on the Interleukin-6.Interleukin-6 (IL-6) is also an inflammatory marker that is widely used in the routine examination of diabetes and coronary atherosclerosis.

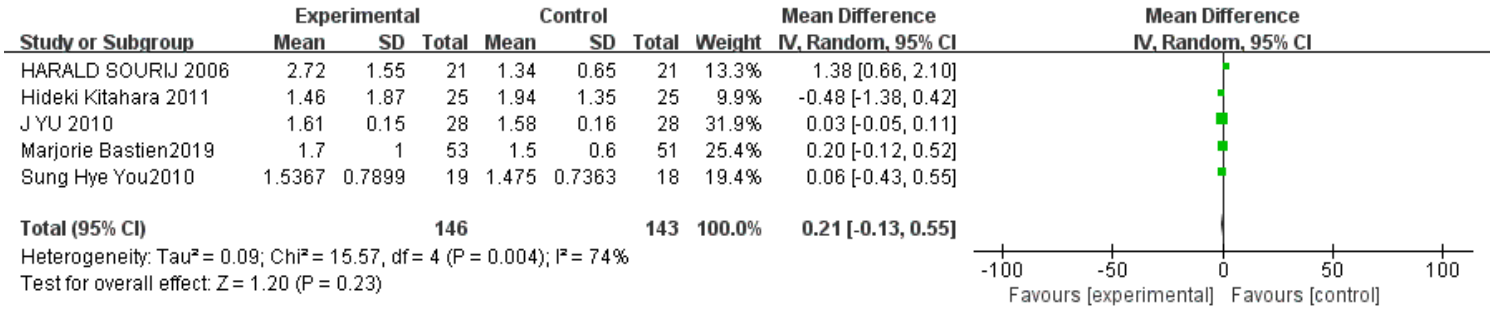

Figure 9

Effect of the TZD on the glycerin trilaurate□TG□.TG is a commonly used biomarker of blood lipid level.

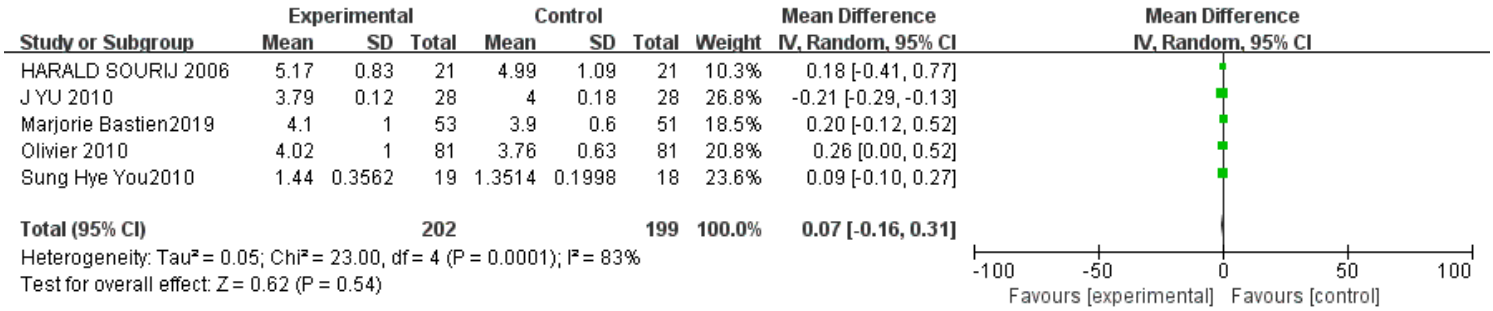

Figure 10

Effect of the TZD on the total cholesterol □TC□TC is a commonly used biomarker of blood lipid level.

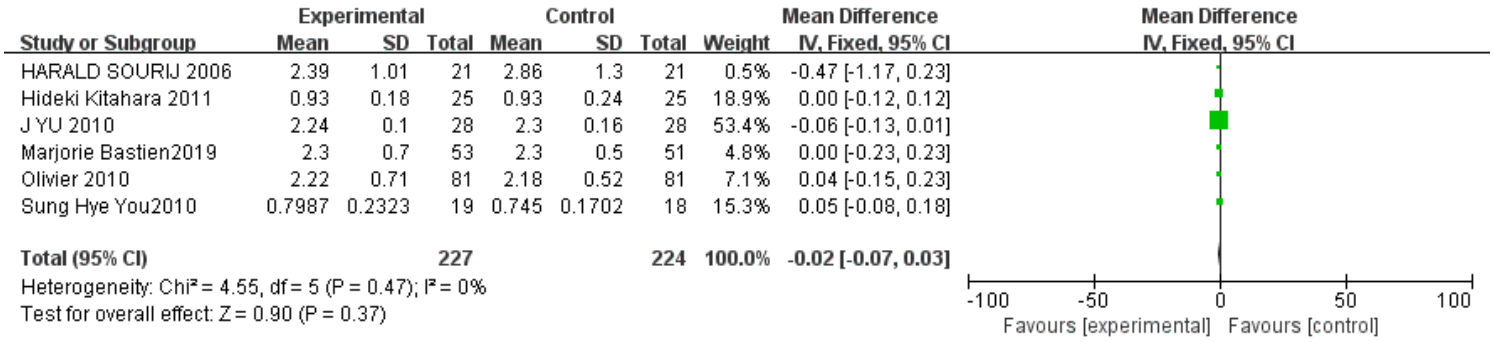

Figure 11

Effect of the TZD on the LDL-C. LDL-C is a commonly used biomarker of blood lipid level.

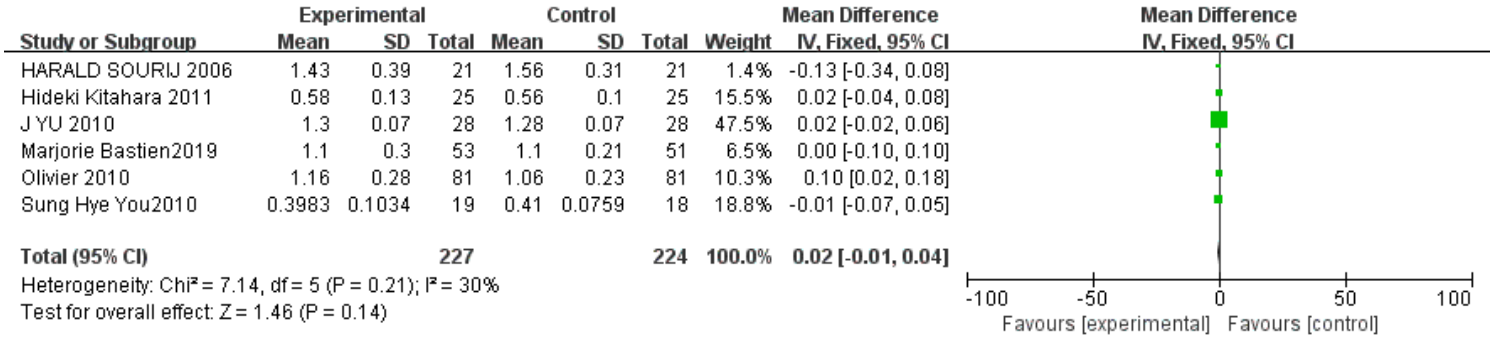

Figure 12

Effect of the TZD on the HDL-C. HDL-C is a commonly used biomarker of blood lipid level.

Supplementary Files

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- Additionalfile1.docx