Metformin in combination with rosiglitazone contribute to the increased serum adiponectin levels in people with type 2 diabetes mellitus

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Abstract. To evaluate how metformin plus rosiglitazone affect serum adiponectin levels in people suffering from type 2 diabetes mellitus (T2DM), 240 patients having T2DM were selected in this cohort study. Included subjects were randomly and equally separated into three subsets: i) Group A (rosiglitazone group); ii) group B (metformin group); and iii) group C (rosiglitazone + metformin group). Furthermore, meta-analysis of previous studies was performed by searching the general search engines and bibliographic databases. Compared with before treatment, the serum amount of adiponectin grew considerably in the three groups after treatment, and the levels in the group C was much greater than those of groups A and B (all $P<0.05$). Corresponding meta-analysis results suggested post-treatment serum adiponectin level to be greater than pretreatment level in T2DM patients ($P<0.001$). Further subgroup analyses indicated that combination therapy of metformin and rosiglitazone may increase the amount of serum adiponectin in T2DM sufferers among the majority subgroups (all $P<0.05$). The combination of metformin and rosiglitazone treatment increased serum adiponectin levels, suggesting that metformin plus rosiglitazone therapy is a suitable choice to treat T2DM.

Introduction

Metformin is medically considered as the only biguanide which is used and recommended as oral anti-diabetic agent, which is crucial for decreasing the levels of plasma glucose (1). As known, metformin has been found to exert an increasing effect on inhibiting hepatic gluconeogenesis, decreasing hyperinsulinemia, reducing protein synthesis, improving insulin sensitivity and enhancing glucose use in the muscle (2,3). Metformin may therefore be applicable for a wide use for the treatment of metabolic syndrome, reducing the risk of cancer and delaying aging (4). In clinical practice, previous evidence has reported that metformin is widely accepted as an effective treatment for diabetes mellitus (DM), and notably to type 2 DM (T2DM) by serving as the first-line therapy (5). Apart from metformin, rosiglitazone is well-known as another valuable anti-diabetic drug which is a member of the thiazolidinedione class of drugs (6). Studies have shown that rosiglitazone has the ability to attenuate inflammatory effects, elicit insulin sensitivity and lower the glucose by serving as the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (7,8). Accordingly, rosiglitazone has an obvious effect on atherosclerosis, inflammation, endothelial dysfunction and T2DM (9).

Adiponectin may be capable of modulating the processes of lipid metabolism and regulating glucose (10). Abundant previous evidence has shown that the lack or dysfunction of adiponectin was proved to be intensely correlated with insulin resistance due to its characteristic as an insulin-sensitizing hormone (11,12). It was well established that T2DM is not only a disease of glucose metabolism, but an inflammatory disease, inflammatory factors have been suggested to be critically implicated (13-15). The abnormal lipid metabolism in patients with diabetes can aggravate the inflammatory reaction. Importantly, adiponectin has been identified to be important for properties as anti-inflammation, insulin-sensitivity and anti-atherosclerosis (16,17). Plasma adiponectin levels present a negative correlation with insulin sensitivity; therefore, it decreases when insulin resistance and diabetes develop (18,19). In addition, adiponectin may result in the reduction of the content of intracellular cholesteryl ester in human macrophages (20). With respect to the above, an obvious increase in adiponectin may suggest the curative effect of metformin and glimepiride in treatment of T2DM.

Metformin has been found to stimulate the secretion of adiponectin and to upregulate the expression of adiponectin

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to some extent (21). Thus, it is shown that the metformin has a certain association with serum adiponectin levels in people suffering from T2DM (22). On the other hand, using the rosiglitazone to treat patients with T2DM may be able to stimulate the production of adiponectin in adipocytes, which means that there may be a certain association between the rosiglitazone and the serum adiponectin levels in patients with T2DM (23). Importantly, recent investigation has shown that therapy of patients with T2DM through metformin as well as rosiglitazone may upregulate serum adiponectin levels obviously by reducing the insulin resistance greatly, so the treatment may be valuable and important to the patients with T2DM (24). To this day, numerous studies have been published indicating that using metformin in combination with rosiglitazone may be a promising treatment regimen for patients with T2DM by affecting the serum adiponectin levels (25,26) while other studies had illustrated contradictory results (27,28). Therefore, we conducted the present investigation on the basis of a clinic-based cohort study and meta-analysis to determine the association between the combined treatment of metformin plus rosiglitazone and the serum adiponectin levels in people suffering from T2DM.

Materials and methods

Ethics statement. Our research process carried out with the presence of human participants conformed to the ethical requirements of the Research Committee of The Third Affiliated Hospital of Guangzhou Medical University (approval no. 2012003) and to the Declaration of Helsinki 1964 (https://www.mendeley.com/research-papers/world-medical-asssociation-declaration-helsinki/) and subsequent amendments. Each participant signed a comprehensive consent form before the investigation.

Subjects. Altogether 240 patients suffering from T2DM were selected and admitted to this cohort study from January 2012 to July 2014. Diagnosis criteria of diabetes was predefined based on the criteria in 2007 by the American Diabetes Association (29) included subjects met the requirements set out below: Fasting plasma glucose (FPG) ≥7.0 mmol/l, or glycosylated haemoglobin A1c (HbA1c) ≥6.5%, or oral glucose tolerance test (OGTT) measured 2 h blood glucose level ≥11.1 mmol/l, or patients with typical high blood sugar or high-blood sugar crisis showed an obvious trend for an increase in random blood glucose level ≥11.1 mmol/l. In addition, in patients without clear hyperglycemia, repeated detection of FBG, HbA1c and OGTT measured 2 h blood glucose were used. There were 164 males and 76 females, aged 32-76 years, with a mean age of 50.50±9.19 years. The duration of disease was 0.4-23.0 months (mean value of 11.40±6.55 years). Patients were enrolled based on the following criteria: i) All patients were free of chronic liver disease; ii) had no hyperthyroidism and other endocrine and metabolic diseases; iii) without bone joint diseases, or bone metastasis cancer affecting calcium and phosphorus metabolism; iv) without severe systemic disease; v) without ketoacidosis or a long time history of bed rest; vi) without hormone, vitamin D_3 and calcium medication history; vii) without administration history of other agents irrelevant to anti-diabetic properties to exclude the influence to serum levels of adiponectin; and viii) selected female patients were post-menopausal women for 10 years. The included subjects were separated at random into three subsets (80 patients in each set) and managed by different treatment regimens. Data generators were used to populate tables with random test data from 1 to 240, counts in multiples of three was subdivided into group A, and the remaining numbers in multiples of two was subdivided into group B, and the last remaining numbers were subdivided into group C, who were treated with rosiglitazone, metformin and rosiglitazone + metformin, respectively.

Clinical data collection and related cytokine detection. Fasting elbow venous blood samples (5 ml) were taken from the subjects in the morning, followed by centrifugation at 2,250 x g for 10 min, serum samples were isolated at 4˚C and followed by plasma glucose and lipid analyses. Furthermore, samples were saved at -20˚C for the measurement of serum adiponectin. All indexes were measured at the beginning of treatment (pretreatment) and 24 weeks after treatment (post-treatment). Body mass index (BMI), waist circumference, waist/hip ratio, FPG, HbA1c, 2 h blood glucose, triglyceride, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase, aspartate aminotransferase, serum total bilirubin and direct bilirubin of all the studied subjects were measured. The levels of adiponectin was examined enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Treatment regimens. All the included patients received dietary intervention and exercise therapy, other drugs affecting plasma glucose of the patients were avoided during the experiment. Medication: i) Group A (rosiglitazone group), taking rosiglitazone (4 mg; GlaxoSmithKline, Middlesex, UK), once a day; ii) group B (metformin group), taking metformin (0.15 g; Beijing Zhonghui Pharmaceutical Co., Ltd., Beijing, China) 3 times a day, the medicines were taken during or after meal to reduce gastrointestinal reactions; and iii) group C (rosiglitazone + metformin group), taking 4 mg rosiglitazone once a day and 0.15 g metformin 2 times a day. Medicine in the three groups were all oral administered lasting for 24 weeks.

Data sources and retrieval strategies. Before March 2016, available literature, assessing the effect of metformin combined with rosiglitazone on serum amount of adiponectin in T2DM sufferers, were obtained via the application of computer datasets and search engines (Embase, Web of Science, PubMed and China National Knowledge Infrastructure). 'Metformin' or 'Dimethylguanylguanidine' or 'Glucophage' or 'Diabex' or 'Dimethylbiguanide' or 'Melbin' or 'Mellitin' or 'Hydrochloride' as well as 'rosiglitazone' or 'rosiglitazone maleate' or 'Avandia' or 'BRL 49653' or 'BRL49653' or 'BRL-49653' as well as 'Adiponectin' or 'adiponectin' or 'Adipocyte Complement-Related Protein 30-kDa' or 'Adipose Most Abundant Gene Transcript 1' or 'ACRP30 Protein' as well as 'Diabetes Mellitus' or 'diabetes' or 'diabetic mellitus' or 'mellitus' or 'type 2 diabetes mellitus' or 'type 1 diabetes mellitus' or 'type 1 diabetes' or 'type 2 diabetes' were utilized as the mesh items and key words. Only articles published in Chinese and English were eligible.

Table I. Comparisons of basic information among groups.

Variables	Group A		Group B		Group C	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment	Pretreatment	Post-treatment
FPG (mmol/l)	7.22±1.62	6.64±1.40[a]	7.29±1.74	6.60±1.35[a]	7.32±1.60	6.24±1.32[a-c]
HbA1c (%)	7.02±1.12	6.54±0.94[a]	7.09±1.03	6.49±0.95[a]	7.08±1.04	6.16±0.89[a-c]
2 h blood glucose (mmol/l)	15.67±2.72	13.57±2.61[a]	15.20±2.43	13.40±2.47[a]	15.42±2.23	11.28±2.34[a-c]
Triglyceride (mmol/l)	5.66±1.78	5.51±1.45[a]	5.58±1.50	5.43±1.43[a]	5.62±1.61	5.12±1.56[a-c]
Cholesterol (mmol/l)	2.44±1.30	2.21±0.90[a]	2.36±1.26	2.17±0.88[a]	2.36±1.33	2.01±0.85[a-c]
HDL (mmol/l)	1.34±0.35	1.22±0.32[a]	1.38±0.37	1.24±0.30[a]	1.35±0.33	1.13±0.25[a-c]
LDL (mmol/l)	3.48±1.27	3.23±1.05[a]	3.46±1.25	3.19±1.12[a]	3.42±1.35	3.11±1.00[a-c]
Alanine aminotransferase (mmol/l)	46.33±20.54	32.81±14.57[a]	45.57±19.69	29.79±13.77[a]	43.68±21.50	24.62±14.21[a-c]
Aspartate aminotransferase (mmol/l)	32.32±15.62	23.90±7.49[a]	31.66±14.21	24.04±7.45[a]	31.22±15.06	20.05±6.90[a-c]
Serum total bilirubin (mmol/l)	28.68±13.60	14.56±4.54[a]	26.90±12.57	13.61±4.24[a]	27.47±14.14	10.44±4.02[a-c]
Direct bilirubin (mmol/l)	3.88±1.38	2.78±1.27[a]	3.75±1.30	2.72±1.24[a]	3.76±1.34	2.51±1.15[a-c]
BMI (kg/m^2)	28.32±6.72	28.11±6.90	28.81±7.23	28.26±6.83[a]	28.76±6.80	27.34±5.52[a-c]
Waist circumference (cm)	93.19±7.70	91.44±14.57	92.48±8.03	90.42±7.56[a]	93.13±7.90	88.21±6.76[a-c]
Waist/hip ratio	0.98±0.05	0.95±0.06	0.94±0.07	0.91±0.06[a]	0.96±0.06	0.86±0.05[a-c]
Adiponectin (ng/ml)	12.08±6.38	21.98±6.56[a]	12.83±4.55	22.51±7.28[a]	12.26±5.68	26.26±7.52[a-c]

[a]Compared to the values before treatment; [b]compared to the values in group A; [c]compared to the values in group B. HbA1c, glycosylated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Inclusion criteria were: i) Studies had to be human-associated studies; ii) designed in a cohort type; iii) had to provide available and adequate data considering serum adiponectin level pre- and post-treatment of metformin and rosiglitazone; and iv) without overlapping data with other studies. And when two or more studies were conducted by the same authors, only the latest and complete study met our consideration standards.

Information extraction and quality estimation. Two researchers (J-M Nie and H-F Li) extracted information separately relied on a standard form, and arrived at a consensus, when there was disagreement, with the third investigator who was specializing in this field. A set of predefined criteria was used to evaluate enclosed research, namely, Critical Appraisal Skills Programmer (CASP) criteria (http://www.casp-uk.net/#!casp-tools-checklists/c18f8).

Statistical analysis. Power analysis was carried out by the Power and Sample Size Calculation (PS) program, we computed the needed sample sizes for a 0.80 probability of determining influence at the predefined level (i.e., α=0.05) for statistical power analysis. A sampling of 240 estimable people for each treatment group would yield nearly 80% power to determine effects at the predefined level (i.e., α=0.05) in groups A-C. Regarding clinical experimental data analysis, statistical analyses were done using SPSS 19.0 statistical software (SPSS, Inc., Chicago, IL, USA). Continuous data are presented as mean ± standard deviation, and t-test was used to confirm the results. For meta-analysis, summary standard mean differences (SMDs) with 95% confidence interval (CI) were used for statistical comparison with the utilization of Z test, which was aggregated utilizing the STATA software, version 12.0 (StataCorp, College Station, TX, USA).

Results and Discussion

Benchmark traits. In group A, there were 56 males as well as 24 females, having a mean age of 52.21±12.62 years, 57 males and 23 females in group B (mean age of 54.18±12.97), and 51 males and 29 females in group C (mean age of 55.59±11.88). The courses of diseases were 11.40±6.64, 10.70±6.96 and 12.20±6.01, respectively, in group A, B and C. There appeared to be only minor differences regarding the age, sex ratio and diseases duration before treatment among the three groups (all P>0.05). Furthermore, no case was eliminated during the treatment period.

Comparison of indices. FPG, HbA1c and 2 h blood glucose all indicated significant decreased tendency among the three groups after treatment than those before treatment, and was the most significant in group C (all P<0.05). Little evident statistical distinction was found between groups A and B with respect to the glucose indices (P>0.05). Besides, triglyceride, cholesterol, HDL and LDL were also suppressed later in the three groups when contrasted with the indices before treatment, significantly decreased tend was found in group C. Furthermore, alanine aminotransferase, aspartate aminotransferase, serum total bilirubin, direct bilirubin were decreased after treatment among groups A-C (all P<0.05), but without statistical distinction between groups A and B (P>0.05) (Table I).

Compared with values before treatment, the BMI, waist circumference and waist/hip ratio decreased significantly in group C than those of the before treatment levels (all P<0.05), but showed no apparent changes in the other two groups (P>0.05). Besides, the BMI, waist circumference and waist/hip ratio decreased obviously in group C after treatment than in groups A and B, with statistical significance (both P<0.05),

but there was no statistical difference regarding the BMI, waist circumference and waist/hip ratio after treatment between groups A and B (P>0.05).

Comparison of serum adiponectin level. Compared with before treatment, the serum amount of adiponectin increased tremendously in the three groups after treatment (all P<0.05), while levels in the group C was significantly higher than the levels of groups A and B (both P<0.05). However, little evident statistical distinction was found between groups A and B regarding serum adiponectin levels after treatment (Table I).

Included studies. Finally, a total of 6 cohort studies were reasonable for the present meta-analysis (4 Asian-based and 2 Caucasian-based studies) metformin between 2006 and 2014, including 267 subjects with T2DM altogether (25-28,30,31). All quality results of the included studies were in moderate to high grade, as shown in Fig. 1.

Association of combination therapy with serum adiponectin level. As shown in Fig. 2A, after treatment serum adiponectin level in T2DM sufferers appeared greater than pretreatment level in those sufferers (SMD=1.27, 95% CI: 0.73-1.81, P<0.001). Subgroup analysis acccording to ethnicity indicated that combination therapy of metformin and rosiglitazone may increase the level of serum adiponectin in T2DM patients among Asians and Caucasians (both P<0.05) (Fig. 2B-D). By using both RIA and ELISA, an increased serum adiponectin level was detected after the treatment of metformin and rosiglitazone in sufferers of T2DM (both P<0.001). Further, the serum level of adiponectin in T2DM sufferers after treatment was greater than the level in the sufferers before treatment in both ≤6 months and >6 months subgroups (both P<0.001).

Sensitivity analysis as well as publication bias. Sensitivity analysis suggested that there was no single study that could have an adverse effect on the overall estimation of the present analyses (Fig. 3A). The graphical funnel plots of those 6 cases appeared symmetrical, and Egger's test implied no publication bias (t=0.96, P=0.368) (Fig. 3B).

Further analysis. This study found that the combination of metformin as well as rosiglitazone has roles in increasing serum level of adiponectin involving in improving glucose and lipid metabolism, liver function indices, as well as body fat mass control, suggesting that metformin plus rosiglitazone therapy is a suitable choice for treating T2DM clinically. The results were confirmed both in the clinic-based cohort study and meta-analysis of this study.

Many types of well-established anti-diabetic drugs exist including metformin, glimepiride and rosiglitazone, also termed as triple-therapy for T2DM; the experimental results manifested that the triple-therapy can significantly increase adiponectin serum levels compared to the combination of metformin + glimepiride, and is efficacious in lessening diabetic cardiomyopathy (32). As presented in this study, the effects of single metformin or rosiglitazone treatment showed significantly lowered efficacies in decreasing glucose and lipid metabolism, liver function, as well as body fat mass indices, which eventually confirmed the combination effect

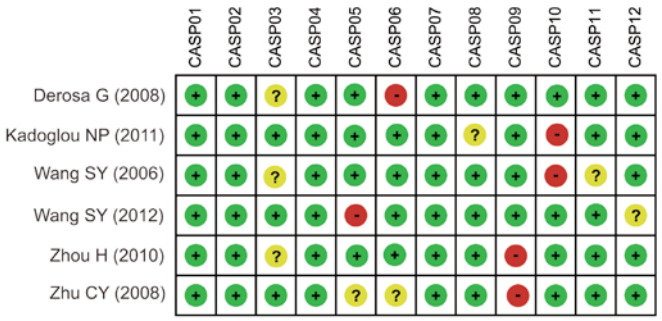

Figure 1. Methodological quality assessment according to the CASP. Green, yes; red, no; yellow, unknown. CASP, Critical Appraisal Skills Programme.

of metformin or rosiglitazone regimens in treating T2DM. The combined therapy of metformin plus rosiglitazone obtained improvement of lipid and glucose metabolism and insulin resistance reduction, as it was previously reported, which elucidating the positive functions of this therapy through downregulating leptin levels and elevating serum levels of adiponectin (33). Importantly and concretely, with respect to the interaction mechanism between metformin and rosiglitazone that have led to the significant improvement in serum adiponectin level, it was considered that adiponectin elevated insulin sensitivity via the stimulation of glucose utilization and increasing free fatty acid oxidation based on the adenosine monophosphate-activated protein kinase (AMPK) signal pathway, besides, PPAR-γ response element (PPRE) is present in the promoter region of adiponectin gene, suggesting an important role of PPAR-γ in regulating the synthesis of adiponectin gene (34,35). Based on the above description of the effect of metformin in modulating AMPK and involving the IR regulation, as well as the pharmacological property of rosiglitazone as one of the compounds of thiazolidinedione, acting as a selective agonist of PPAR-γ (36,37), such combination may significantly promote the synthesis and secretion of adiponectin contributing to increasing level of adiponectin and improving insulin sensitivity. Another published study demonstrated that T2DM patients suffer the complication of cardiovascular disease, however, the oral intake of metformin plus rosiglitazone was useful for alleviating hyperglycemic syndrome and reducing blood pressure by mediating glucose uptake in skeletal muscle and increasing adiponectin expression to assist insulin activities (38).

In view of previous opinions from multiple aspects, we put forward that the relationship between metformin plus rosiglitazone application and adiponectin levels in T2DM patients is significant and this drug therapy is advantageous to suppress hepatic glycogenesis and increase adiponectin level to enhance insulin sensitivity, which effectively relieve weight gain and blood pressure. Li *et al* came up with an opinion in line with our study result that the combining therapy of metformin and rosiglitazone is a more effective method for treating T2DM compared with metformin monotherapy and the dominant effects resulted in insulin release, different normal β-cell function, thereby improving body fat and ameliorating T2DM severity (39). In addition, further meta-analysis also confirmed the results that combination of metformin and rosiglitazone treatment increased serum adiponectin levels in a majority of

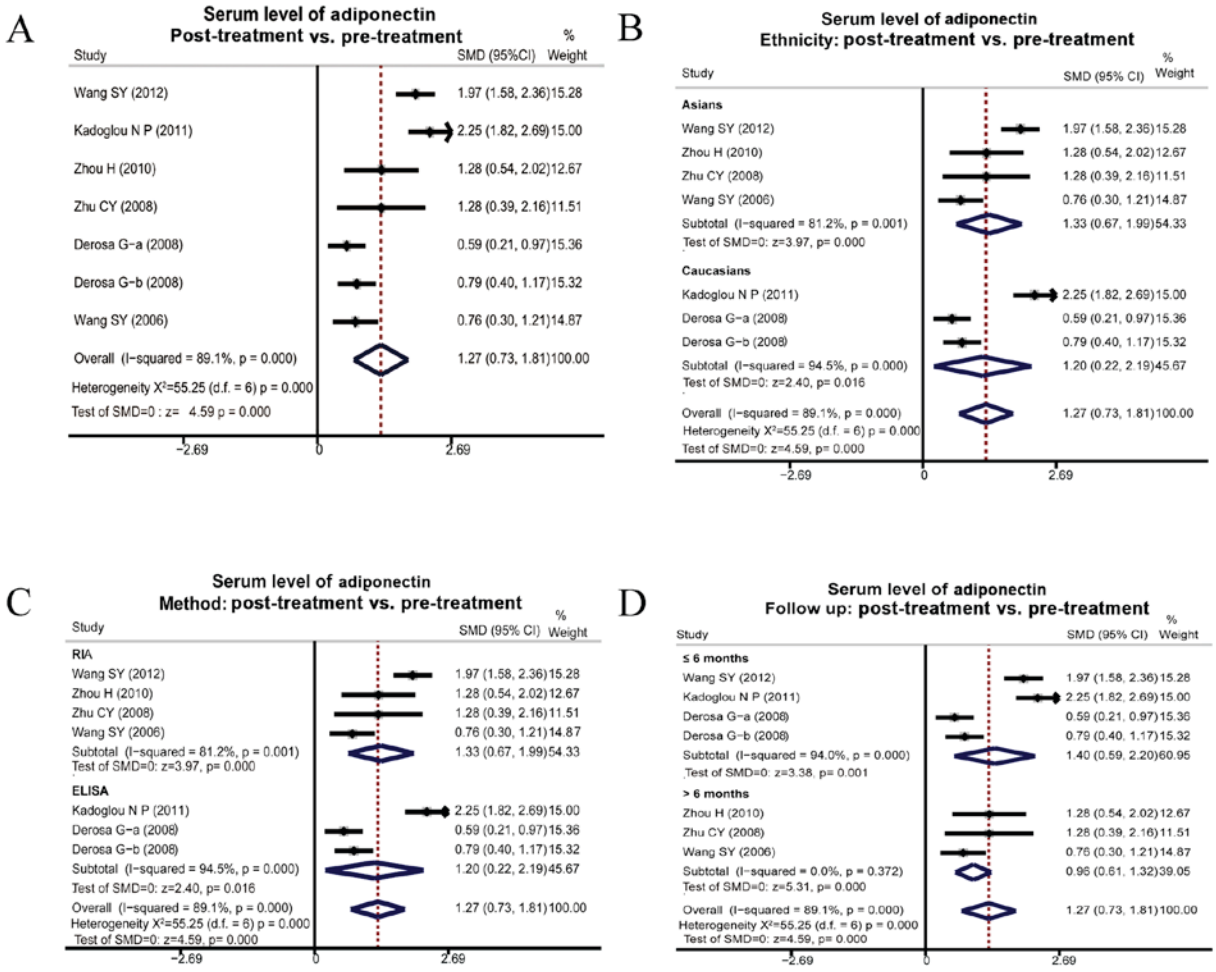

Figure 2. (A) Forest plots for the relationships exploration of the effects of metformin plus rosiglitazone on serum adiponectin levels in sufferers of T2DM. (B-D) Subgroup discussion by ethnicity, detection methods and continuation exploring the effects of metformin plus rosiglitazone on serum adiponectin levels in sufferers of T2DM. T2DM, type 2 diabetes mellitus.

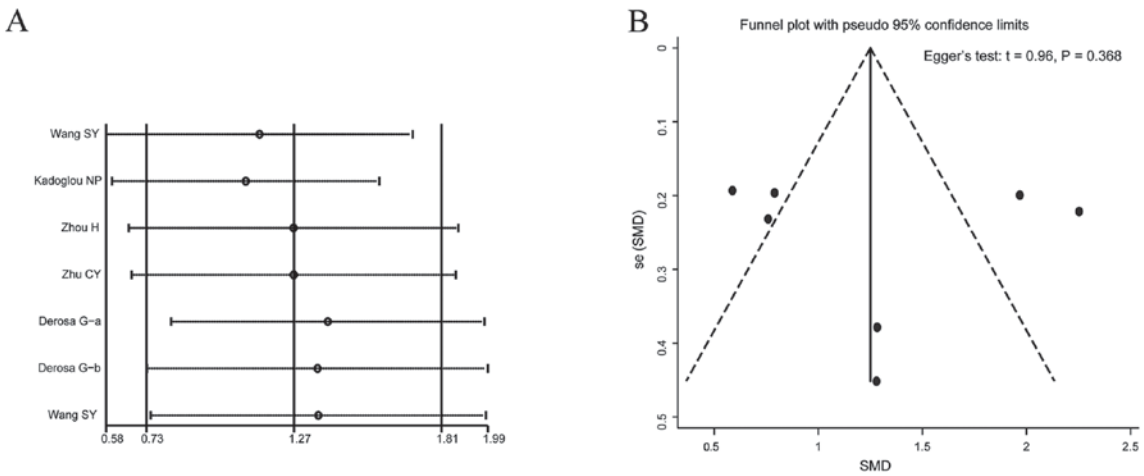

Figure 3. (A) Sensitivity analysis performance assessing whether single study could affect the whole results in our meta-analysis. (B) Publication bias exploration of the summary standard mean differences coefficients based on investigating the effects of metformin plus rosiglitazone on serum adiponectin levels in sufferers of T2DM. T2DM, type 2 diabetes mellitus.

subjects, suggesting that metformin plus rosiglitazone therapy is a suitable choice for the treatment of T2DM.

In conclusion, our findings revealed that combination of metformin and rosiglitazone increased serum level of adiponectin, suggesting that metformin plus rosiglitazone therapy is a suitable choice for the treatment of T2DM. Importantly, continuous studies with large sample size evaluating the biological significance of concrete adiponectin

levels as well as other sensitive biomarkers in T2DM patients receiving metformin and rosiglitazone or other medicines are recommended in future studies.

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