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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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META-ANALYSIS

Indirect comparison of efficacy and safety of chiglitazar and thiazolidinedione in patients with type 2 diabetes: A meta-analysis

Chu Lin, Zong-Lin Li, Xiao-Ling Cai, Sui-Yuan Hu, Fang Lv, Wen-Jia Yang, Li-Nong Ji

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Abstract

BACKGROUND

Chiglitazar is an emerging pan-agonist of all peroxisome proliferator activated receptors (PPAR)-α, δ and γ, and has therapeutic potential for type 2 diabetes (T2D). However, to date, no clinical studies or meta-analyses have compared the efficacy and safety of chiglitazar and traditional PPAR-γ agonist thiazolidinediones (TZDs). A meta-analysis concerning this topic is therefore required.

AIM

To compare the efficacy and safety of chiglitazar and TZD in patients with T2D.

METHODS

PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, *Reference Citation Analysis* and *Clinicaltrial.gov* websites were searched from August 1994 to March 2022. Randomized controlled trials (RCTs) of chiglitazar or TZD *vs* placebo in patients with T2D were included. Indirect comparisons and sensitivity analyses were implemented to evaluate multiple efficacy and safety endpoints of interest.

RESULTS

We included 93 RCTs that compared TZD with placebo and one that compared chiglitazar with placebo. For efficacy endpoints, the augmented dose of chiglitazar resulted in greater reductions in hemoglobin (Hb)A1c [weighted mean difference (WMD) = -0.15%, 95% confidence interval (CI): -0.27 to -0.04%], triglycerides (WMD = -0.17 mmol/L, 95%CI: -0.24 to -0.11 mmol/L) and alanine aminotransferase (WMD = -5.25 U/L, 95%CI: -8.50 to -1.99 U/L), and a greater increase in homeostasis model assessment-β (HOMA-β) (WMD = 17.75, 95%CI: 10.73-24.77) when compared with TZD treatment. For safety endpoints, the risks of hypoglycemia, edema, bone fractures, upper respiratory tract infection, urinary tract infection, and weight gain were all comparable between the augmented dose of chiglitazar and TZD. In patients with baseline HbA1c ≥ 8.5%, body mass index ≥ 30 kg/m^2 or diabetes duration < 10 years, the HbA1c reduction and HOMA-β

increase were more conspicuous for the augmented dose of chiglitazar compared with TZD.

CONCLUSION
Augmented dose of chiglitazar, a pan-activator of PPARs, may serve as an antidiabetic agent with preferable glycemic and lipid control, better β-cell function preserving capacity, and does not increase the risk of safety concerns when compared with TZD.

Key Words: Chiglitazar; Thiazolidinedione; Glycemic control; β-cell function; Drug safety

Core Tip: This is the first indirect meta-analysis comparing efficacy and safety of chiglitazar and thiazolidinediones (TZDs). In patients with type 2 diabetes, compared with TZDs, chiglitazar induced favorable glycemic and lipidemic control, preserved β-cell function, without increasing safety concerns.

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INTRODUCTION

Thiazolidinediones (TZDs) are hypoglycemic agents for type 2 diabetes (T2D) that characteristically alleviate insulin resistance (IR) to improve glycemic control[1]. TZDs are able to activate the peroxisome proliferator activated receptors (PPARs), which are mainly distributed in adipose tissue[2]. They also enhance sensitivity to insulin in target tissues through multiple downstream mechanisms including promoting fatty acid storage in adipose tissue and reducing free fatty acids (FFAs)[3], releasing insulin-sensitizing adipokines such as adiponectin[4], and suppressing excretion of IR-inducing cytokines such as tumor necrosis factor (TNF)-α[5]. Therefore, TZDs are effective in patients with traits of IR[6].

In previous clinical trials in patients with T2D, besides the favorable glycemic control[7], TZD also decreased the index of homeostasis model assessment of insulin resistance (HOMA-IR)[8], which indicated improved insulin sensitivity. However, the potential adverse events of TZD (including edema[9], heart failure[10], bone fracture[11], weight gain[2,9] and hepatic injury[12]) raised concerns. It has been reported that TZD lead to overactivation of PPAR-γ, which accelerates weight increase through facilitating adipocyte differentiation[1], and promotes water–sodium retention *via* more epithelial sodium channel expression in kidney tubules[13]. Other detrimental adverse effects including increased risks of bone fracture and heart failure were also found related to selective and excess PPAR-γ activation[1,13].

Due to the safety concerns, further applications of TZD in T2D treatment are therefore limited and whether the specific benefits of TZD outweigh the risks remains controversial. However, chiglitazar, a pan-agonist of PPAR-α, PPAR-δ and PPAR-γ[14], has been developed as a promising agent with improved therapeutic efficacy and safety by activation of multiple PPARs[15]. PPAR-α is mainly expressed in skeletal muscle and liver which regulates fatty acid metabolism[16], and its activation is associated with improved lipid profiles[17]. PPAR-δ is distributed widely in somatic cells, whose activation participates in elevated insulin sensitivity[18] and reverses metabolic abnormalities[15]. PPAR-α activation might also be associated with a reduced risk of heart failure[19], while PPAR-δ agonists have been reported to alleviate diabetic osteoporosis by promoting macrophage polarization[20].

Subsequently, with comprehensive activation of PPAR subtypes, chiglitazar may outperform TZD in terms of efficacy and safety in the management of T2D. However, to our knowledge, there have been no head-to-head randomized clinical trials (RCTs) directly comparing the efficacy and safety of chiglitazar and TZD. Hence, we conducted an indirect comparison meta-analysis using the data from RCTs comparing chiglitazar and TZD with placebo in patients with T2D.

MATERIALS AND METHODS

Study design and registration

This systematic review and indirect meta-analysis was conducted in line with the criteria of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol[21]. Registration has been accomplished on International Prospective Register of Systematic Reviews (PROSPERO) platform as CRD42022334206.

Data sources and searches

In conformation with the recommendations in the Cochrane Handbook for Systematic Reviews for Meta-analysis, we implemented a systematic literature retrieval in Pubmed, Medline, Embase, Cochrane Central Register of Controlled

Trials, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and *Clinicaltrial.gov* websites for RCTs of chiglitazar or TZD treatment with placebo comparator in patients with T2D, which were published between August 1994 and March 2022. The search strings were as follows: Chiglitazar, pioglitazone, rosiglitazone, troglitazone, englitazone, thiazolidinedione, TZD, randomized controlled trial, placebo, efficacy, safety, T2D. The references in retrieved articles were also screened to thoroughly identify available and eligible RCTs.

Study selection and data extraction

The inclusion criteria of this indirect meta-analysis were: (1) Studies conducted in patients with T2D; (2) studies comparing chiglitazar or TZD with placebo; and (3) studies with reports of efficacy or safety outcomes. Two investigators (CL and ZL) independently screened articles by titles, abstracts and full text, excluded duplicate and ineligible studies, evaluated the quality and risk of bias with the Cochrane risk of bias tool, and extracted data from eligible studies. The collected data included: Study design (drug exposure, study duration, sample size in experimental and control arms); publication information (first author and publication year); baseline characteristics of patients [age, baseline hemoglobin (Hb)A1c, body mass index (BMI), sex ratio, ethnicity, and diabetes duration]; efficacy parameters [changes in HbA1c, fasting blood glucose (FBG), HOMA-IR, HOMA-β, total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)]; and safety parameters (measurements of weight gain; incidence of hypoglycemia, edema, heart failure, bone fracture, upper respiratory tract infection, and urinary tract infection). Required data were primarily abstracted from the original articles or attached supplementary materials. The *Clinicaltrials.gov* website was subsequently searched if data were not available in articles and supplementary materials. Discrepancies were resolved by reaching a consensus with another joint investigator (XC).

Risk of bias assessment

The risk of bias in enrolled RCTs was assessed with the Cochrane Collaboration tool[22]. The evaluating measurements included random sequence generation, allocation concealment, blinding of participants and care-givers, missing outcome data, selective outcomes reporting, and other bias. Each domain was evaluated by degrees of the existing risks of bias, including "definitely yes", "probably yes", "definitely no", "probably no" according to the instruction[22].

Data synthesis and analysis

The primary efficacy endpoint was defined as indirect comparison of changes in HbA1c after treatment with chiglitazar or TZD in comparison with placebo. The indirect comparisons for other efficacy parameters (including FBG, HOMA-IR, HOMA-β, TG, LDL-C, HDL-C, ALT and AST) were interpreted as exploratory efficacy endpoints. The primary safety endpoint was defined as indirect comparison of the incidence of hypoglycemia after treatment with chiglitazar or TZD in comparison with placebo. Indirect comparisons for the incidence of other adverse events including edema, heart failure, bone fracture, upper respiratory tract infection, and urinary tract infection, and measurement of weight gain were interpreted as exploratory safety endpoints. Subgroup analyses with regard to baseline characteristics including age, baseline HbA1c, BMI, male percentage, predominant ethnicity, diabetes duration, follow-up duration, and monotherapy or combination therapy were performed to further characterize the influences of these potentially associated factors on the outcomes. Caucasian predominance was defined as the percentage of Caucasian > 50% of the participants. Correspondingly, Asian predominance was defined as the percentage of Asian > 50% of the participants. Meanwhile, we also conducted subgroup analyses concerning different TZD subtypes in indirect comparisons for changes in HbA1c and TG to further compare the efficacy between chiglitazar and different subtypes of TZD. Meta-regression analyses evaluating the potential correlation between baseline characteristics (including age, male percentage, BMI, diabetes duration, study duration, and baseline HbA1c) and the study outcomes were also conducted in the TZD treatment group (since the chiglitazar treatment group only involved one RCT, when the meta-regression analysis could not be implemented).

Prior to producing an indirect estimate of the treatment effect of chiglitazar *versus* TZD, we primarily checked the adequacy of such synthesis[23,24]. Homogeneity of the results from the placebo group as a common comparator for the indirect comparison was first evaluated among included studies. Whether the treatment effects were sufficiently homogeneous to be pooled within each comparison of chiglitazar *vs* placebo and TZD *vs* placebo was evaluated. We also qualitatively assessed the trials for patient characteristics and design features for comparability, based on which, the subsequent sensitivity analyses were performed to control the potential confounding effects.

To perform the indirect comparison, we firstly calculated the pooled treatment effect estimates of chiglitazar *vs* placebo and TZD *vs* placebo through regular meta-analysis statistical methods. Afterwards, the indirect comparison was implemented by synthesizing the pooled treatment effect estimates of each treatment group compared with placebo. Results of continuous variables in this indirect meta-analysis were presented as the weighted mean difference (WMD) with 95% confidence intervals (CIs). For discontinuous variables, the risk ratios (RRs) with 95%CIs were calculated and rendered. The heterogeneity of the included studies was evaluated by Higgins I^2 statistics. $I^2 \geq 50\%$ represented a high level of heterogeneity; otherwise, a low level of heterogeneity level was considered. A random-effects model was uniformly adopted for data analyses. Publication bias was assessed with the funnel plot. Statistical significance was considered at $P < 0.05$. Statistical analyses were principally completed by Review Manager version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) and STATA version 12.0 (Stata Corp., College Station, TX, United States).

RESULTS

Characteristics and quality assessments of included studies

There were 94 RCTs included in this meta-analysis, including one comparing chiglitazar with placebo (166 participants in the chiglitazar arm *vs* 202 in the placebo arm), and 93 comparing TZD with placebo (15580 participants in the TZD arm *vs* 14706 in the placebo arm). The RCT of chiglitazar investigated two doses, where 32 mg and 48 mg were defined as the standard and augmented doses, respectively. The TZDs involved in this meta-analysis included pioglitazone, rosiglitazone and troglitazone. The selection and inclusion process of eligible studies is summarized in the flow chart (Figure 1).

Baseline characteristics of included studies are recorded in Supplementary Table 1. The quality assessments were conducted with Cochrane instruments (Supplementary Table 2), which indicated low overall risks of bias in included studies. There was one RCT with high risk of frequent missing data, while all RCTs were with low risks in inadequate randomization sequence generation, inadequate allocation concealment, selective outcome reporting, masking patients and caregivers, and masking outcome assessors. The publication bias was evaluated by funnel plots, which displayed even distributions in most of the endpoints but an asymmetric distribution for the endpoint of edema (Supplementary Figure 1).

Indirect comparisons of effects of augmented dose of chiglitazar versus TZD on efficacy endpoints

For glycemic control, compared with placebo, chiglitazar (WMD = -1.05%, 95%CI: -1.10 to -1.00%) and TZD (WMD = -0.90%, 95%CI: -1.00 to -0.79%) significantly reduced HbA1c in patients with T2D (Supplementary Figure 2). The indirect comparison indicated a greater reduction in HbA1c with the augmented dose of chiglitazar compared with TZD (WMD = -0.15%, 95%CI: -0.27 to -0.04%). Both chiglitazar (WMD = -1.55 mmol/L, 95%CI: -2.08 to -1.09 mmol/L) and TZD (WMD = -2.05 mmol/L, 95%CI: -2.32 to -1.77 mmol/L) were associated with significantly reduced FBG level when compared with placebo. The reduction in FBG was comparable between the augmented dose of chiglitazar and TZD (WMD = 0.50 mmol/L, 95%CI: -0.04 to 1.03 mmol/L).

With respect to lipid profiles, chiglitazar (WMD = -0.38 mmol/L, 95%CI: -0.40 to -0.36 mmol/L) and TZD treatment (WMD = -0.21 mmol/L, 95%CI: -0.27 to -0.15 mmol/L) were effective in lowering TG levels in patients with T2D compared with placebo. The indirect comparison indicated greater TG reduction with chiglitazar compared with TZD (WMD = -0.17 mmol/L, 95%CI: -0.24 to -0.11 mmol/L). Although chiglitazar and TZD were both associated with increased LDL-C compared with placebo, greater LDL-C elevation was observed in patients with augmented dose chiglitazar compared with TZD (WMD = 0.13 mmol/L, 95%CI: 0.09 to 0.17 mmol/L). Both chiglitazar (WMD = 0.09 mmol/L, 95%CI: 0.086 to 0.094 mmol/L) and TZD (WMD = 0.10 mmol/L, 95%CI: 0.08 to 0.11 mmol/L) contributed to elevated HDL-C levels compared with placebo. Such effects on HDL-C were comparable between augmented dose of chiglitazar and TZD (WMD = -0.01 mmol/L, 95%CI: -0.02 to 0.14 mmol/L).

Although the effectiveness of reducing HOMA-IR index was validated in patients treated with augmented dose chiglitazar (WMD = -0.94, 95%CI: -0.99 to -0.89) and TZD (WMD = -1.81, 95%CI: -2.30 to -1.33) compared with placebo, chiglitazar might underperform with respect to HOMA-IR reduction compared with TZD (WMD = 0.87, 95%CI: 0.38-1.37). However, chiglitazar was associated with a profound elevation in HOMA-β index compared with placebo (WMD = 16.64, 95%CI: 16.23-17.05), which was not observed in patients with TZD treatment compared with placebo (WMD = -1.11, 95%CI: -8.12 to 5.90). The indirect comparison further indicated the superiority of chiglitazar in HOMA-β improvement (WMD = 17.75, 95%CI: 10.73-24.77) over TZD.

For liver enzymes, compared with placebo, chiglitazar treatment was associated with significantly decreased ALT (WMD = -6.60 U/L, 95%CI: -9.19 to -4.01 U/L) and AST level (WMD = -3.00 U/L, 95%CI: -4.66 to -1.34 U/L). TZD was associated with significantly decreased ALT level (WMD = -1.35 U/L, 95%CI: -8.32 to -0.62 U/L) but did not significantly change AST level (WMD = -0.03 U/L, 95%CI: -6.44 to -6.40 U/L) in patients with T2D. By indirect comparison, the augmented dose of chiglitazar outperformed TZD for ALT reduction (WMD = -5.25 U/L, 95%CI: -8.50 to -1.99 U/L), whereas chiglitazar and TZD exhibited similar effects on AST levels (WMD = -2.98 U/L, 95%CI: -9.61 to 3.65 U/L) (Figure 2).

Sensitivity analyses showed that chiglitazar reduced HbA1c more prominently compared with TZD in patients with age ≥ 60 years (WMD = -0.30%, 95%CI: -0.41 to -0.18%), baseline HbA1c ≥ 8.5% (WMD = -0.44%, 95%CI: -0.58 to -0.30%), BMI ≥ 30kg/m^2 (WMD = -0.24%, 95%CI: -0.40 to -0.08%), and duration of diabetes < 10 years (WMD = -0.16%, 95%CI: -0.31 to -0.02%) (Supplementary Table 3). The increase in HOMA-β after chiglitazar treatment was significantly greater than that after TZD treatment in patients with baseline HbA1c ≥ 8.5% (WMD = 26.36, 95%CI: 8.80-43.93), BMI ≥ 30 kg/m^2 (WMD = 29.42, 95%CI: 19.34-39.50) and duration of diabetes < 10 years (WMD = 26.36, 95%CI: 8.80-43.93) (Supplementary Table 3). Sensitivity analyses of TZD subtypes indicated that the greater reduction in HbA1c in patients treated with augmented dose of chiglitazar *vs* TZD was mainly shown by comparison between chiglitazar 48 mg once daily and rosiglitazone 4 mg once daily (WMD = -0.39 %, 95%CI: -0.67 to -0.11 %). The greater reduction in TG after treatment by chiglitazar was mainly shown by comparison between chiglitazar 48 mg once daily and rosiglitazone 4 mg once daily (WMD = -0.58 mmol/L, 95%CI: -0.86 to -0.30 mmol/L) as well as comparison between chiglitazar 48 mg once daily and rosiglitazone 8 mg once daily (WMD = -0.22 mmol/L, 95%CI: -0.36 to -0.08 mmol/L) (Supplementary Table 3).

Indirect comparisons of the effects of augmented dose of chiglitazar vs TZD on safety endpoints

Compared with placebo, chiglitazar did not increase the risk of hypoglycemia (RR = 2.43, 95%CI: 0.45-13.12), which was elevated in patients with TZD treatment (RR = 1.72, 95%CI: 1.48-2.01) (Supplementary Figure 3). However, the indirect comparison suggested a non-significant difference in risk of hypoglycemia between chiglitazar and TZD treatment (RR = 1.42, 95%CI: 0.26-7.68). Both chiglitazar (WMD = 2.50 kg, 95%CI: 1.93-3.07 kg) and TZD (WMD = 2.15 kg, 95%CI: 1.51-2.79

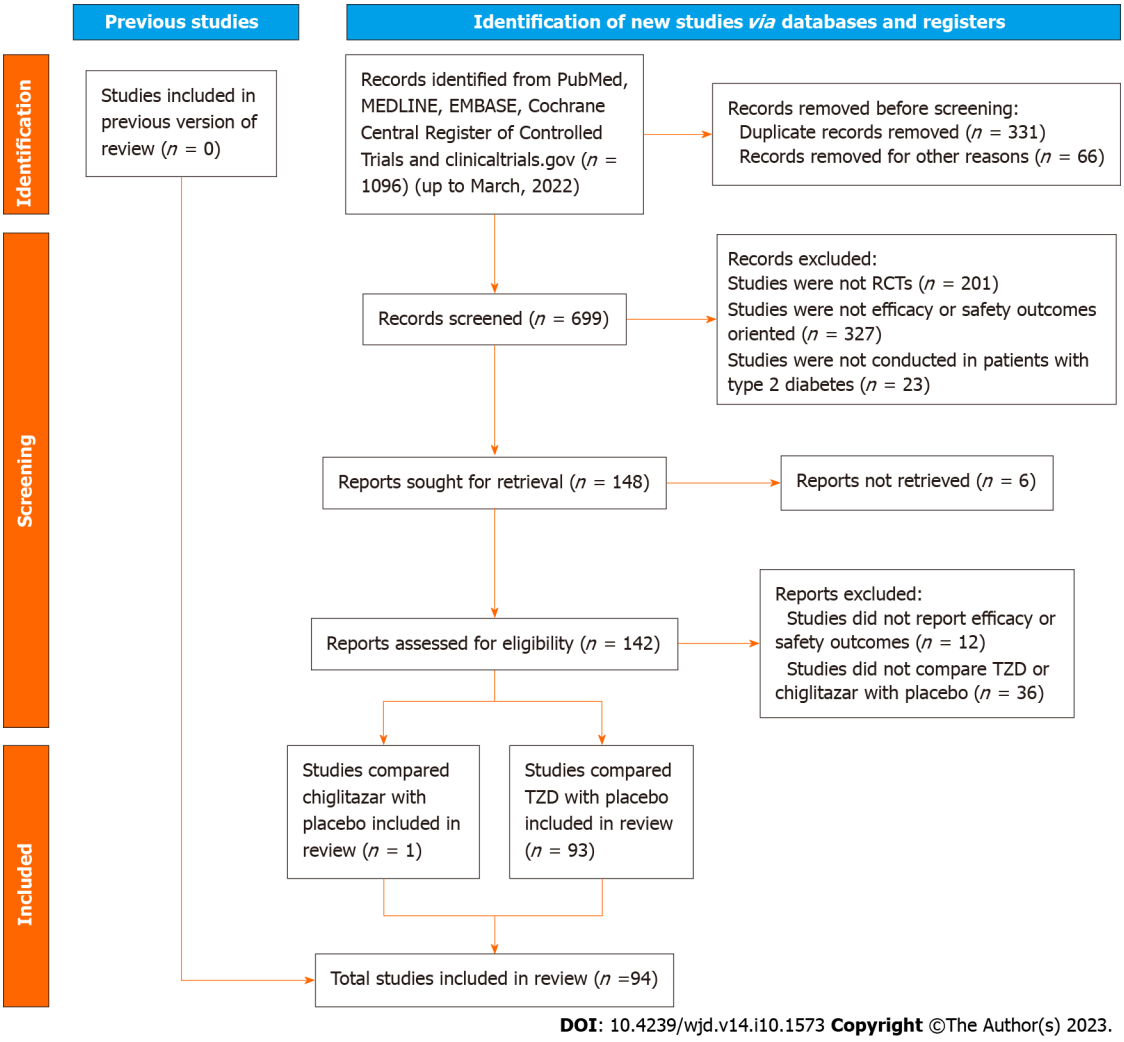

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Figure 1 Flow chart of this indirect meta-analysis.

kg) were associated with significantly increased body weight compared with placebo, but the weight gain was comparable between chiglitazar and TZD treatment in patients with T2D (WMD = -0.04 kg, 95%CI: -0.16 to 0.08 kg). Although heart failure was defined as an exploratory safety endpoint in this research, since no case of heart failure was reported in the chiglitazar or placebo treatment arms, we were unable to conduct an indirect comparison of the incidence of heart failure after treatment with chiglitazar or TZD (Figure 3). Compared with placebo, chiglitazar (RR = 20.67, 95%CI: 1.20-355.40) and TZD (RR = 2.04, 95%CI: 1.72-2.42) were both associated with significantly elevated risks of edema in patients with T2D. The risk of edema was comparable between chiglitazar and TZD (RR = 10.18, 95%CI: 0.59-175.98). The incidence of other adverse events, including bone fractures, upper respiratory tract infection and urinary infection, was comparable between chiglitazar/TZD and placebo, when indirect comparison also indicated a non-significant difference between chiglitazar and TZD treatment (Figure 3). Subgroup analyses of safety endpoints also conferred negative findings (Supplementary Table 3).

Indirect comparison of effects of standard dose of chiglitazar versus TZD on efficacy and safety endpoints

In patients treated with standard dose of chiglitazar, we observed significantly decreased HbA1c, FBG, TG, HOMA-IR index and ALT, and significantly elevated LDL-C, HDL-C and HOMA-β index compared with placebo, which was consistent with the results of treatment with augmented dose of chiglitazar. However, the indirect comparison suggested comparable change of HbA1c, TG and ALT levels after treatment with chiglitazar or TZD in comparison with placebo in patients with T2D. For safety endpoints, compared with placebo, standard dose of chiglitazar was not associated with increased risk of hypoglycemia. The increased risk of edema with augmented dose of chiglitazar became non-significant after treatment with standard dose of chiglitazar. Indirect comparison indicated comparable risks of safety concerns between standard dose of chiglitazar and TZD treatment, which was consistent with the results of the indirect compassion between augmented dose of chiglitazar and TZD treatment. The detailed results are shown in Supplementary Figure 4.

Meta-regression analyses

Meta-regression analyses showed that in patients under TZD treatment, male percentage (β = 0.011, 95%CI: 0.002-0.021, *P*

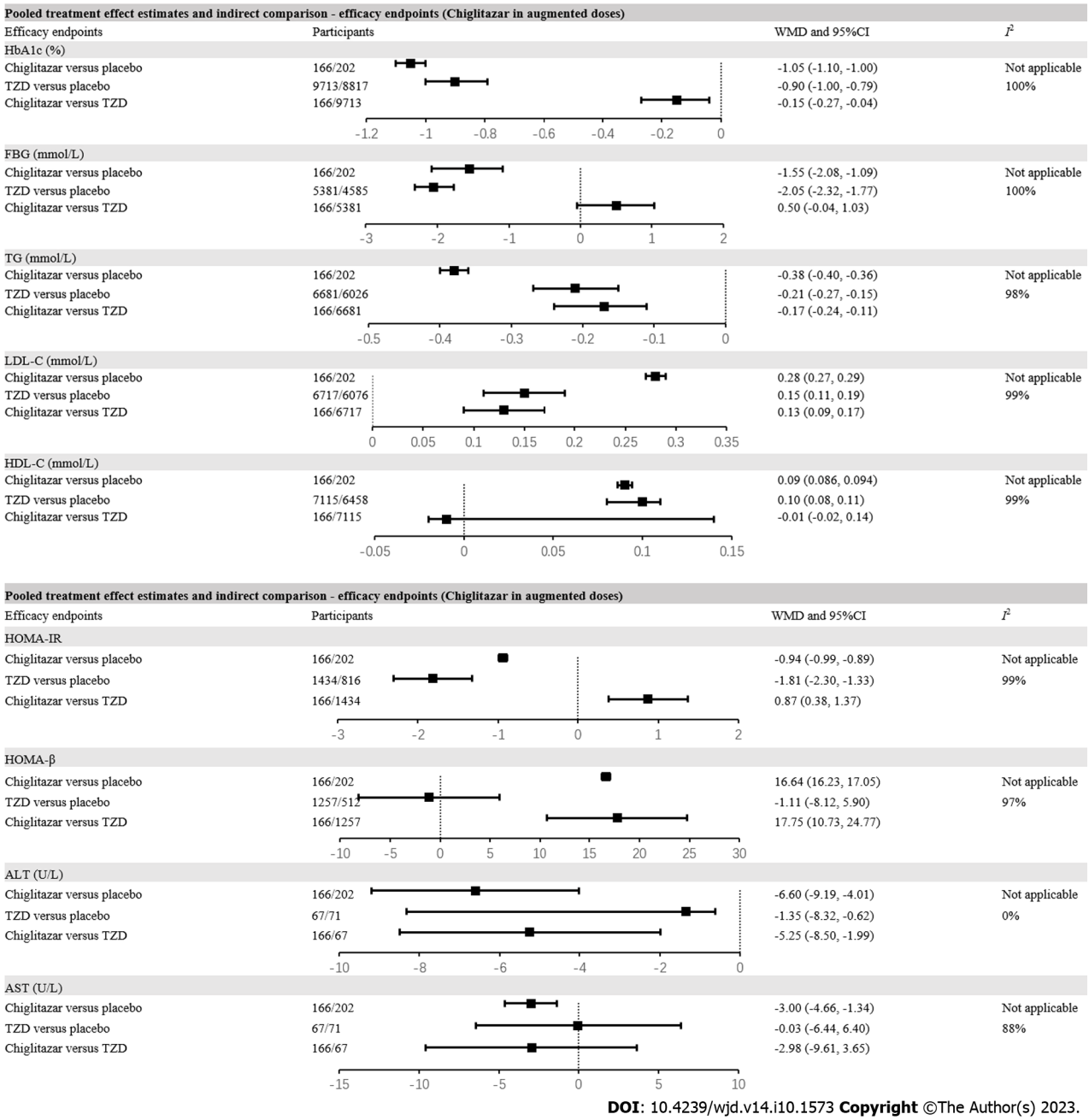

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Figure 2 The forest plot exhibiting pooled effect estimates and indirect comparison between chiglitazar and thiazolidinediones on efficacy endpoints including hemoglobin A1c, fasting blood glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, homeostasis model assessment of insulin resistance, homeostasis model assessment of β cell function, alanine aminotransferase and aspartate aminotransferase. HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals; TZD: Thiazolidinedione.

= 0.019) and baseline HbA1c (β = -0.320, 95%CI: -0.427 to -0.212, *P* = 0.0001) were significantly correlated with the change in HbA1c, when baseline HbA1c (β = -0.578, 95%CI: -0.768 to -0.388, *P* = 0.0001) and BMI (β = -0.249, 95%CI: -0.442 to -0.055, *P* = 0.013) were significantly correlated with changes in FBG and TG, respectively. Male percentage also exhibited a significant linear association with the change in LDL-C (β = -0.006, 95%CI: -0.012 to -0.0001, *P* = 0.046), and baseline HbA1c showed a significant linear association with the change in HOMA-IR (β = -0.573, 95%CI: -1.112 to -0.034, *P* = 0.039) (Supplementary Table 4).

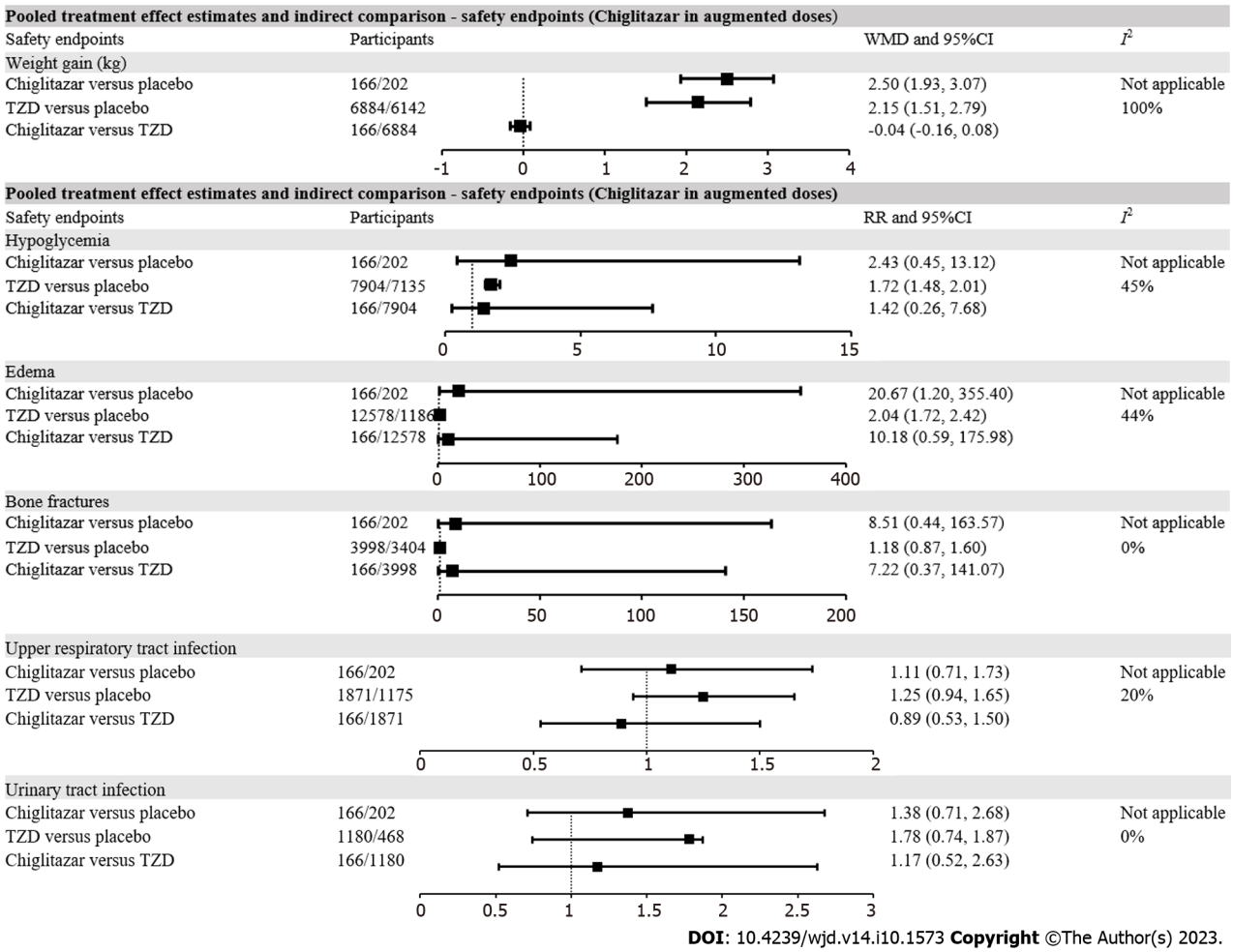

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Figure 3 The forest plot exhibiting pooled effect estimates and indirect comparison between chiglitazar and thiazolidinediones on safety endpoints including weight gain, hypoglycemia, edema, bone fractures, upper respiratory tract infection and urinary tract infection. HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals; TZD: Thiazolidinedione.

DISCUSSION

To our knowledge, this is the first comprehensive meta-analysis comparing the efficacy and safety of chiglitazar and TZD. According to this meta-analysis, augmented doses of chiglitazar outperformed TZD treatment for HbA1c, TG and ALT reduction and HOMA-β index elevation, and conferred greater LDL-C elevation and less HOMA-IR reduction in patients with T2D. For safety endpoints, the risks of hypoglycemia, edema, heart failure, bone fractures, upper respiratory tract infection and urinary tract infection, and weight gain were all comparable between augmented doses of chiglitazar and TZD. Further sensitivity analyses indicated that in patients with age ≥ 60 years, baseline HbA1c ≥ 8.5%, BMI ≥ 30 kg/m^2 or diabetes duration < 10 years, the reduction in HbA1c and improvement in HOMA-β were more conspicuous with augmented doses of chiglitazar compared with TZD.

Chiglitazar and TZD, as hypoglycemic agents, both lowered blood glucose level with mutual pivotal mechanisms of activating PPAR-γ[14,25]. PPAR-γ activation could ameliorate hyperglycemia by enhancing glucose transporter-1 and -4 of adipocytes, which facilitated glucose ingestion in adipose tissues[26]. Therefore, PPAR-γ activation mediated glucose lowering effects in both chiglitazar and TZD. However, since chiglitazar acted as a pan-agonist of PPAR-α, PPAR-δ and PPAR-γ, the hypoglycemic capacity of chiglitazar may also be derived from the activation of other PPARs. PPAR-α was distributed widely in liver, skeletal muscle, heart and adipose tissues, and its activation accelerated fatty acid uptake and oxidation and lipoprotein assembly[27], which resulted in decreased FFA and TG levels and fat accumulation. The lipid-modulating effects of PPAR-α activation attenuated lipidic toxicity for β cells[28] and inhibited gluconeogenesis from excess lipids[29], which improved overall glycemic control. PPAR-α activation was also reported to promote glucose metabolism and ketogenesis[27], which increased glucose consumption and thereby lowered blood glucose. Activation of PPAR-δ facilitated glucose metabolism through the pentose phosphate pathway[25] and increased basal metabolic rate [29] to reduce blood glucose. PPAR-α and PPAR-δ activation improved β-cell function[30,31], which lowered glycemia independent of IR remission[27]. The details are elaborated in the next section.

Apart from their hypoglycemic effects, chiglitazar and TZD reduced the serum TG level, for which PPAR-γ activation served as the mutual mechanism. Activation of PPAR-γ was associated with lipid uptake, lipid droplet formation, and adipocyte differentiation[25,44] in adipose tissues, as well as lipid oxidation in skeletal muscle and liver, which resulted in decreased circulating FFA and TG levels[32]. PPAR-γ activation promoted synthesis of bio-active proteins including fat-specific protein 27 and monoacylglycerol O-acyltransferase 1, which participated in lipid uptake and storage[29,33]. PPAR-γ activation also increased preadipocyte differentiation and functionalization, thus accelerating lipogenesis and consumption of lipids[34].

In our study, the augmented doses of chiglitazar outperformed TZD with respect to TG reduction. The enhanced hypolipidemic effects of chiglitazar may also have been derived from activation of PPAR-α and PPAR-δ. PPAR-α was identified as a regulator of lipid metabolism, whose activation increased lipid uptake and transport, fatty acid oxidation, lipoprotein assembly and TG accumulation in the liver[27]. PPAR-α activation also facilitated cytochrome P4504A production, which participated in hydroxylation of fatty acids and thereby reduced TG synthesis[35]. The PPAR-α agonists fibrates lowered TG levels and have been extensively used in patients with dyslipidemia[36], which confirms the hypolipidemic activity of PPAR-α activation. PPAR-δ activation was associated with fatty acid transport, lipid oxidation and decreased fatty acid release[25], and fat combustion and thermogenesis contributed to overall lipid reduction. Mice treated with PPAR-δ agonists had significantly lowered TG levels[37], indicating PPAR-δ activation had the potential to improve TG profiles. Therefore, chiglitazar may result in greater TG reduction compared with TZD, and the additional hypolipidemic effects may be derived from PPAR-α and PPAR-δ activation.

We found that chiglitazar and TZD treatment was associated with elevated LDL-C and HDL-C concentrations, which was more pronounced with augmented doses of chiglitazar compared with TZD. It was indicated that PPAR-α and PPAR-γ activation could facilitate reversed cholesterol transportation and lipoprotein exchange, and therefore increased plasma LDL-C and HDL-C levels[38]. Activation of either PPAR resulted in significant HDL-C elevation in previous *in vivo* experiments[39-41], whereas the changes in LDL-C under PPAR agonist treatment were inconsistent[42,43]. The underlying mechanisms have also not been fully demonstrated, and further investigations on the correlations between PPARs and cholesterol are required.

The activation of PPAR-α, PPAR-δ and PPAR-γ was associated with ameliorated nonalcoholic fatty liver disease *via* improved lipidemic and glycemic control[29]. The transfer of fat and lipids from viscera to peripheral tissues was facilitated by PPAR-α activation, which also relieved steatosis of hepatocytes[27]. We observed significantly decreased ALT levels after treatment with augmented doses of chiglitazar compared with TZD. The greater ALT reduction with chiglitazar may also have resulted from alleviated liver injuries with the favorable lipidemic, glycemic control and fat distribution through additional activation of PPAR-α and PPAR-δ.

IR and attenuation of β-cell function have been identified as the central pathophysiology of T2D; therefore, ameliorating IR and postponing β-cell failure have become important strategies in retarding T2D progression[44]. PPAR-γ activation contributed to adipocytes remodeling by virtue of facilitating apoptosis of visceral insulin-resistant adipocytes and generation of subcutaneous insulin-sensitive adipocytes[45]. It was also demonstrated that PPAR-γ activation lowered secretion of adipocytokines and chemokines, which contributed to IR[46]. PPAR-γ activation also prevented β-cell dysfunction by improving glycemic control and lipid metabolism, which attenuated glucotoxicity and lipotoxicity in islets[47,48]. PPAR-γ activation also inhibited the production of inflammatory cytokines, including TNF-α, interleukin (IL)-1 and IL-6, which mitigated islet inflammation and preserved β-cell function[49,50].

PPAR-α and PPAR-δ agonists improved insulin sensitivity in *in vitro* studies[51-53]. The insulin-sensitizing effects of PPAR-α and PPAR-δ were mostly circuitous and not as well-established as those of PPAR-γ. Since the interactions to PPAR-α, PPAR-δ and PPAR-γ of chiglitazar were generally balanced, the stimulating intensity to PPAR-γ might be relatively decreased when compared with TZD[25]. Therefore, the relief of IR by chiglitazar might also have been attenuated when compared with that of TZD. Although PPAR-γ activation was potentially able to preserve β-cell function as noted above, we observed comparable HOMA-β index alteration between TZD treatment and placebo. However, HOMA-β index was significantly elevated by chiglitazar treatment at both standard and augmented doses when compared with placebo and TZD. According to previous researches, HOMA-β index elevation may be attributed to the activation of PPAR-α and PPAR-δ. PPAR-α activation was associated with islet adaptation to starvation, which enhanced glucose utilization and insulin secretion[54]. Glucose-induced insulin secretion was also promoted by PPAR-α activation [55], especially in response to hyperglycemia[56]. PPAR-α activation stimulated insulin secretion through inhibition of Ca^{2+} signaling[57]. The islet-preserving effects of PPAR-δ have also received extensive attention. Many studies have indicated that PPAR-δ activation significantly improved islet function in mice, with the potential of elevating β-cell mass [58], alleviating β-cell lipoapoptosis[59], and reducing inappropriate baseline secretion[60]. Favorable glycemic and lipidemic control, and ameliorated chronic inflammatory states derived from PPAR-α and PPAR-δ activation may also participate in preservation of β-cell function[44]. However, the effects of PPAR-γ, PPAR-α and PPAR-δ activation on β-cell function have not been fully characterized. Further research on the specific mechanisms of preservation of β-cell function by chiglitazar and PPAR activation is required.

Although TZD significantly improved glycemic and lipidemic control and relieved IR, the clinical utilization of TZD was limited by the increased risk of adverse events. The adverse events related to TZD were primarily hypoglycemia[10], weight gain[9], edema[9], congestive heart failure[10], and bone fracture[11]. Since chiglitazar may ameliorate the centralized and excess PPAR-γ activation presented in TZD[22], and potentially exert beneficial effects through PPAR-α and PPAR-δ activation, it was expected that the safety risks could be attenuated in chiglitazar treatment in contrast to TZD. However, in this meta-analysis, we observed significantly increased risks of weight gain and edema with both chiglitazar and TZD compared with placebo. Subsequent indirect comparisons exhibited comparable risk of hypoglycemia, weight gain, edema, bone fracture, upper respiratory tract infection and urinary tract infection between chiglitazar and TZD. The safety of PPAR-α and PPAR-δ activation was not shown[61]. Clinical trials of chiglitazar were

rare, which made it difficult to thoroughly evaluate safety outcomes. Further researches are required to comprehensively assess the safety features and potential mechanisms in chiglitazar.

A number of baseline characteristics are potentially associated with the effects of chiglitazar and TZD in patients with T2D, including age, sex, glycemic control status (baseline HbA1c), BMI and diabetes duration. According to the meta-regression analysis, male percentage, BMI and baseline HbA1c were linearly associated with several glycemic and lipidemic control outcomes. The potential influence of these baseline characteristics on study results should therefore be cautiously considered when interpreting the outcomes of this study. Meanwhile, in this indirect comparison meta-analysis, reduction in HbA1c and improvement of HOMA-β index were more prominent for treatment with augmented doses of chiglitazar compared with TZD for patients with baseline HbA1c ≥ 8.5% (poorly controlled diabetes), BMI ≥ 30 kg/m^2 (obese) or diabetes duration < 10 years (short T2D duration).

In patients with poorly controlled diabetes and frequent hyperglycemia, the systematic metabolic disorders appeared to be more severe[62]. Chiglitazar outperformed TZD in improving lipid profiles and accelerating glucose consumption [49,56]. Therefore, chiglitazar could have achieved better glycemic control and protection of β-cell function through better relief of metabolic disorders, which improved glucose consumption and decreased lipotoxicity to islets.

For patients with obesity, the lipid-modifying effects of chiglitazar may have synergistically improved glycemic control [44]. It would be more effective for chiglitazar to preserve β-cell function in obese patients as their β-cell function was generally better than that in patients who were non-obese[63]. Furthermore, compared with long-established T2D, the severities of metabolic turbulence, glycemic or lipidemic disorder, and deterioration of β-cell function were lower in patients with shorter diabetes duration, which were more reversible with chiglitazar treatment[63].

This study had some limitations. Firstly, this research was based on the statistical approach of indirect comparison. Secondly, since the RCTs had different study designs and populations, the resultant endogenous heterogeneity should not be ignored. To control the heterogeneity, we implemented multiple sensitivity analyses concerning underlying associated factors to minimize the confounding effects. Moreover, there was only one eligible RCT investigating chiglitazar available for the indirect comparison, when the sample size and data abundance were limited. Considering the potential bias, the results and conclusions in this indirect comparison meta-analysis should be interpreted with caution. The comparison should be updated with enriched RCT data of chiglitazar in the future. There was no heart failure event reported in the RCT of chiglitazar; therefore, the indirect comparison of heart failure incidence between chiglitazar and TZD was not possible in this study. More investigations evaluating safety outcomes of chiglitazar, especially heart failure, are still needed.

CONCLUSION

Through pan-activation of PPAR-α, PPAR-δ and PPAR-γ, chiglitazar may serve as a promising therapeutic agent for T2D with preferable glycemic and lipid control, additional β-cell function preservation, and favorable tolerance for augmented doses when compared with TZD.

ARTICLE HIGHLIGHTS

Research background

Chiglitazar as a pan-agonist of peroxisome proliferator activated receptor (PPAR)-α, δ and γ, has the potential to induce better glycemic and lipidemic control than the PPAR-γ agonist thiazolidinediones (TZDs) in patients with type 2 diabetes (T2D).

Research motivation

Currently, there are no clinical studies or meta-analyses comparing the efficacy and safety of chiglitazar and TZD. A meta-analysis is required to further address this topic.

Research objectives

To compare the efficacy and safety of chiglitazar and TZD in patients with T2D.

Research methods

Randomized controlled trials (RCTs) of chiglitazar or TZD *vs* placebo in patients with T2D were retrieved. Indirect comparisons and sensitivity analyses were implemented to evaluate the efficacy and safety endpoints of interest.

Research results

We included 93 RCTs comparing TZD with placebo and one comparing chiglitazar with placebo. For efficacy endpoints, the augmented dose of chiglitazar, compared with TZD, resulted in greater reductions in hemoglobin A1c, triglycerides and alanine aminotransferase levels, and greater homeostasis model assessment of β cell function elevation. For safety endpoints, the risks of hypoglycemia, edema, bone fractures, upper respiratory tract infection, urinary tract infection, and weight gain were all comparable between the augmented dose of chiglitazar and TZD.

Research conclusions

Chiglitazar, a pan-activator of PPARs, may exhibit preferable glycemic and lipid control, and β-cell function preservation, with no additional safety concerns with augmented doses compared with TZD in patients with T2D.

Research perspectives

Chiglitazar has potential for T2D treatment. However, more investigations evaluating safety outcomes of chiglitazar, especially heart failure, are still needed.

FOOTNOTES

Author contributions: Ji LN and Cai XL were responsible for the study concept and designed the systematic review protocol; Lin C and Li ZL performed the study selection and data extraction; Lin C and Li ZL performed the statistical analyses; Lin C, Li ZL and Cai XL prepared the outlines and wrote the manuscript; All authors contributed to the critical revision of manuscript drafts.

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