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Change in left ventricular diastolic function after pioglitazone treatment in patients with type 2 diabetes mellitus

A protocol for systematic review and meta-analysis

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Abstract

Background: Pioglitazone is currently used as an anti-diabetic agent and can reduce cardiovascular events in in patients with type 2 diabetes mellitus (T2DM). Left ventricular diastolic dysfunction has been recognized as an early manifestation of myocardial dysfunction in T2DM patients. This systematic review and meta-analysis aimed to investigate changes in the left ventricular diastolic function after the treatment of pioglitazone.

Methods: A systematic literature search of PubMed, Embase, and the Cochrane Library until May 2021 with keywords pioglitazone and left ventricular diastolic function was performed in accordance with the meta-analysis of observational studies in epidemiology guidelines and preferred reporting items for systematic reviews and meta-analyses statement. Three reviewers independently selected the studies and extracted data. Quality assessment of the included studies was undergone. A fixed effects model was used to calculate overall effect sizes. Subgroup analyses were subsequently performed. A fixed effects model was used to calculate the overall effect size. Subgroup analyses were then performed.

Results: Seven studies with 233 patients were investigated. We found pioglitazone significantly improved hemoglobin A1c (%) in patients with T2DM and left ventricular diastolic function had an improvement tendency (weighted mean difference [WMD], 0.03; 95% confidence interval [CI], 0.01–0.05, $P < .01$) despite moderate heterogeneity ($I^2 = 66\%$). Subsequent subgroup analysis indicated that left ventricular diastolic function were significantly improved (WMD, 0.20; 95% CI, 0.12–0.29, $P < .001$) in T2DM patients whose average age < 55 after receiving pioglitazone treatment. However, in T2DM patients with mean age ≥ 55 years, there was no significant improvement of left ventricular diastolic function (WMD, 0.02; 95% CI, 0–0.04, $P = .04$).

Conclusion: Pioglitazone treatment significantly improved left ventricular diastolic function in type 2 diabetic patients with a mean age of < 55 years, but did not improve left ventricular diastolic function in patients with a mean age of ≥ 55 years.

Abbreviations: CI = confidence interval, HbA1c = hemoglobin A1c, RCT = randomized clinical trial, T2DM = type 2 diabetes mellitus, WMD = weighted mean difference.

Keywords: left ventricular diastolic function, pioglitazone, systemic review and meta-analysis, T2DM

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex group of chronic metabolic diseases characterized by elevated blood sugar levels. Long-term T2DM may cause multiple organ damage, including serious damage to the heart, blood vessels, eyes, kidneys and nerves.[1]

Adults with T2DM have 2- to 3-fold increased risk of cardiovascular disease, including heart failure, angina, myocardial infarction, and stroke, than adults without diabetes.[2] Heart failure is not only a major cause of morbidity and mortality from cardiovascular disease, but also an ominous sign in patients with T2DM, and 50% of those with T2DM and heart failure die within 5 years.[3] Left ventricular diastolic dysfunction has been recognized as an early manifestation of myocardial dysfunction, and it is associated with adverse cardiovascular outcomes in T2DM patients.[4] Delaying or preventing left ventricular diastolic dysfunction could reduce hospitalization and mortality in patients with T2DM.[5]

The diabetic heart disease has been postulated to lose its metabolic flexibility because of myocardial insulin resistance,

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

This meta-analysis was performed in accordance with the PRISMA and the Cochrane Handbook guidelines. An ethics statement is not applicable because this study is based exclusively on published literature. This study protocol conforms to the provisions of the Helsinki Declaration as revised in 2013.

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and this is associated with myocardial lipid accumulation, inflammation, increased collagen formation, myocardial stiffness, and a noncompliant left ventricular. Thiazolidinediones are potent insulin sensitizers in skeletal muscle that enhance myocardial glucose uptake in patients with insulin-mediated T2DM. It has been reported to have various effects in addition to a hypoglycemic action and an ameliorating effect on insulin resistance. Improvement of abnormal lipid and protein metabolism, an anti-inflammatory effect, improvements in dyslipidemia and endothelial dysfunction, an anti-atherogenic action, and an inhibitory effect on oxidative stress have been reported.[6–9]

There are 2 common thiazolidinediones, rosiglitazone and pioglitazone. Rosiglitazone is thought to increase cardiovascular risk.[5–7] In contrast, previous studies have shown that when pioglitazone is used to treat patients with type 2 diabetes, there is also a significant reduction in cardiovascular events.[6] Some studies have shown that pioglitazone can improve left ventricular diastolic function,[7–9] but other studies have reported that pioglitazone has no effect on left ventricular diastolic function.[10–13] The duration of pioglitazone treatment was 16 to 24 weeks and the dose was 15 to 45 milligrams.[11–13]

Left ventricular diastolic function is often evaluated by *E*/*A* ratio on echocardiography and MRI. Peak E is the first peak of blood flow from the left atrium to the left ventricle, and peak A is the second peak of blood flow from the left atrium to the left ventricle. Normally $1 < E/A < 2$, when the ventricle diastole, suction is stronger, so the E peak is higher than the A peak. However, when the diastolic function of the heart is impaired, the diastolic pressure does not decrease significantly, and the peak value of E will be reduced, so $E/A < 1$. When $E/A > 2$, it indicates decreased cardiac compliance and severe diastolic dysfunction.

To date, there has been no meta-analysis to settle this dispute. Therefore, we performed this systematic review and meta-analysis to determine the relationship between pioglitazone and left ventricular diastolic function. Furthermore, we attempted to find the potential cause for these conflicting results.

2. Methods

This systematic review and meta-analysis was conducted and reported following the meta-analyses and systematic reviews of observational studies guidelines for this analysis.[14] The included studies are searched in accordance with the preferred reporting items for systematic reviews and meta-analyses statement.[15]

2.1. Databases and search strategy

A systematic literature search was carried out by 2 authors using 3 online databases, PubMed, EMBASE, and the Cochrane Library up to May 2021. The following medical subject headings terms and text words were used in our original meta-analysis: Pioglitazone, Poglitazone Hydrochloride, AD4833, U72107A, Left Ventricular End-Diastolic Volume, Left Ventricular Diastol, Left Ventricular Diastolic Function, Type 2 diabetes mellitus. Three authors independently reviewed and cross-checked the articles. All the authors agreed that the relevant studies were qualified. We also browsed the references of included papers for potentially relevant publications. Disagreements among the reviewers were resolved by consensus.

2.2. Study selection and criteria

Inclusion criteria were as follows: trials on patients with type 2 diabetes; studies published in English; studies conducted on human subjects; trials examining left ventricular diastolic function before and after the treatment of pioglitazone; and trials that reported at least 1 dispersion measure for treatment groups of pioglitazone.

Exclusion criteria were as follows: animals studies; studies investigating non-pioglitazone interventions; comments, letters, reviews and meta-analyses; data not presented as mean ± standard deviation; and trials lacking necessary data required for left ventricular diastolic function analyses.

2.3. Data extraction and quality assessment

The studies that met the conditions of this meta-analysis were independently browsed by 3 evaluators, and then the corresponding data were extracted into the pre-designed form. If there was a discrepancy, the reviewers assessed the data together to reach a consensus.

The following data were extracted: study characteristics (first author, country, publication year, types of study designs, number of study participants), patients' characteristics (average age, sex ratio, hemoglobin A1c [HbA1c,%]), time of therapy, drug dosage, method of measurement of *E*/*A*, outcomes (value of *E*/*A* before and after the treatment of pioglitazone).

We used the Newcastle-Ottawa Scale[16] to evaluate the quality of the included observational cohort studies. The quality assessment criteria were as follows: whether the patients included in the study really represented all people in the population who had treatment with pioglitazone; whether the non-exposed group was from the same population as the pioglitazone group; whether the type 2 diabetes cases were typical; whether left ventricular diastolic function had been known at start of study; whether the study considered the comparability of pioglitazone and non-pioglitazone groups in design and statistical analysis; whether the results of the study had file records; whether the follow-up time for the population was sufficiently long for outcomes to occur; and whether the follow-up in pioglitazone group was complete. The maximum score attainable was 9 (the maximum score of v. was 2) and studies with a score equal to or higher than 6 were considered to be eligible for our meta-analysis. Details are shown in Figure 1.

As for randomized clinical trials (RCTs), we used Cochrane Collaboration's risk of bias tool with Review Manager version 5.3 to assess their quality. The quality evaluation criteria included: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. the risk bias of each study was evaluated at 3 levels: "high, unknown, or low risk bias." The results of the evaluations were placed in a risk of bias summary. Details are shown in Figure 2.

2.4. Data synthesis and analysis

A fixed effect model was used to calculate the weighted mean differences (WMDs) and 95% confidence intervals (CIs) for the value of *E*/*A* before and after the treatment of pioglitazone.[17] Cochran's Q (chi-square) test was used to quantify the heterogeneity, and the I^2 statistic was used to assess the extent of inconsistency: $I^2 > 50\%$ is considered substantial heterogeneity.[18]Publication bias was assessed by Funnel plot (shown in Fig. 3).

Subgroup analysis according to average age, drug dosage, HbA1c, time of therapy, method of measurement of *E*/*A*, and types of study designs was performed and used to detect potential heterogeneity.

For most tests, A 2-sided P value of $< .01$ was defined as statistical significance. All data was analyzed with Review Manager (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) statistical software.

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow - up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total scores
Clarke et al. 2014[13]	☆	★	★	★	★★	★	★	★	8
Clarke et al. 2017[11]	☆	★	★	☆	★★	★	★	★	7
Ordu et al. 2010[10]	★	★	★	★	★☆	★	★	★	8
Terui et al. 2006[12]	★	★	☆	★	★★	★	★	☆	7

Figure 1. Quality assessment of observational cohort studies.

3. Results

3.1. Literature search

A total of 333 potential articles were identified from the 3 databases. After duplicates were removed, the titles and abstracts of 286 records were independently screened by 2 reviewers, resulting in the selection of 40 articles and then a more detailed assessment of their qualifications. There were 2 studies whose data were repetitive.[8,19] Finally, 7 articles were selected for inclusion in this meta-analysis.[7–13] The detailed steps of the literature search are presented in Figure 4.

3.1.1. Study characteristics. These 7 selected studies were published from 2006 to 2017 and total included 233 patients with type 2 diabetes mellitus. The characteristics of the studies are presented in Table 1. Two studies were carried out in America[11,12] and 1 study was conducted in Japan.[12] Two were in Turkey.[9,10] One was in Netherlands[8] and 1 was in Greece.[7]The sample size of the trials ranged from 12 to 49. Three studies were RCT[7–9] and 4 were Cohort studies.[10–13] The duration of pioglitazone treatment was 16 to 24 weeks and the dose was 15 to 45 milligrams. *E/A* were examined by the means of Echocardiography and MRI. Quality assessment of the included studies is presented in Figure 1 (for cohort studies) and Figure 2 (for RCT).

3.1.2. Overall analysis.

3.1.2.1. HbA1c outcomes. Pioglitazone significantly improved HbA1c (%) in patients with T2DM (WMD, 0.62; 95% CI, 0.55–0.68, $P < .01$) although with high heterogeneities of $I^2 = 77$ (shown in Fig. 5a). Therefore, a sensitivity analysis was performed by random effects model to exclude data that led to significant heterogeneity (pioglitazone improves ventricular diastolic function in patients with diabetes mellitus: a tissue Doppler study[10]), and still found a significant decrease in HbA1c in patients with T2DM (WMD, –0.60; 95% CI, –0.53 to –0.66, $P < .01$) without a significant heterogeneity ($I^2 = 0\%$) (shown in Fig. 5b), which indicated that the heterogeneity did not affect the results.

3.1.2.2. Cardiovascular outcomes. As demonstrated in Figure 5c, the *E/A* ratio was higher after treatment of pioglitazone than pretherapy levels (WMD, 0.03; 95% CI, 0.01–0.05, $P < .01$), implying that pioglitazone improved left ventricular diastolic function in patients with T2DM. However, the WMD from studies that exhibited significant heterogeneity was assessed by a fixed effect model ($I^2 = 66\%$, $P = .007$). No Publication bias was found in funnel plot.

3.1.2.3. Subgroup analysis. Subgroup analysis was performed to explore the source of the heterogeneity. We divided these studies into 2 subgroups: mean age < 55 and mean age ≥ 55. The mean age < 55 subgroup consisted of 3 studies[10–12] and the results showed that left ventricular diastolic function after treatment of pioglitazone were significantly improved (WMD, 0.20; 95% CI, 0.12–0.29, $P < .001$) without a significant heterogeneity ($I^2 = 0$). The mean age ≥ 55 subgroup consisted of 4 studies[7–9,12] and the analysis showed that there was no difference in left ventricular diastolic function after treatment of pioglitazone (WMD, 0.02; 95% CI, 0–0.04, $P = .04$) and the heterogeneity was not significant ($I^2 = 0\%$). Test for subgroup differences: $I^2 = 93.5\%$ ($P < .01$). Details are shown in Figure 5d. These results showed no evidence of heterogeneity and explained part of the problem of heterogeneity in the full analysis.

In the subsequent analysis, we analyzed other subgroups classified by pioglitazone dosage (≤30 mg or > 30 mg), HbA1c (<7%

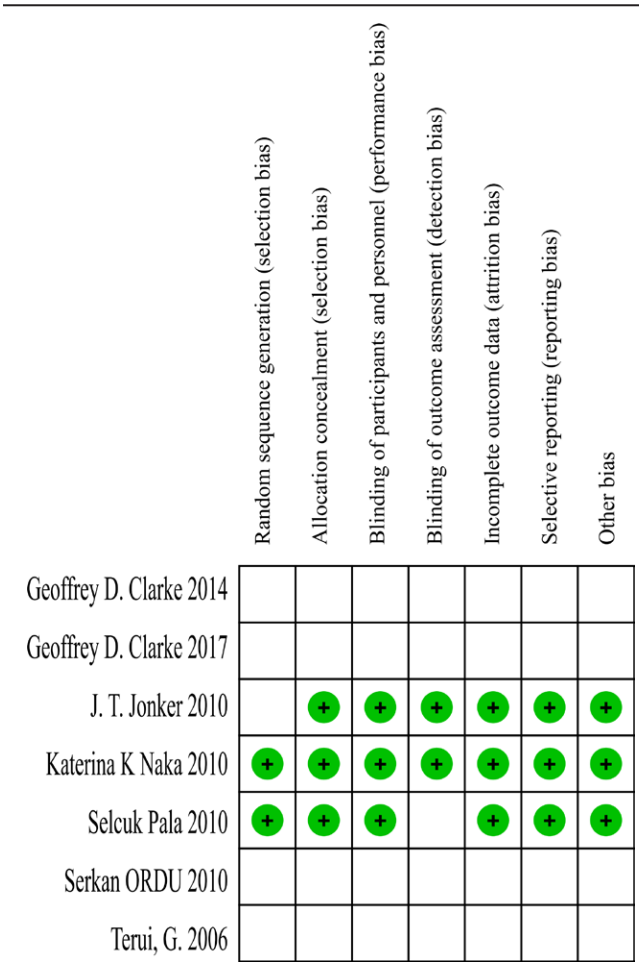

Figure 2. Risk of bias summary of 7 RCTs. RCT = randomized controlled trial.

or > 7%), measuring method (echocardiography or MRI), types of study designs (RCT or cohort study), however, as illustrated in Table 2, the outcomes showed either no significance or high heterogeneity based on the evidence presented.

4. Discussion

In this meta-analysis, we found an improvement in left ventricular diastolic function with pioglitazone treatment. Using subgroup analysis, we attempted to seek the source of heterogeneity in left ventricular diastolic function (*E*/*A*) after pioglitazone treatment.

The thiazolidine derivative pioglitazone, considered as a peroxisome proliferator-activated receptor γ activator, is currently used in the treatment of T2DM.[20,21] It has been reported to have various effects in addition to its hypoglycemic effects and its role in improving insulin resistance. Improvement of abnormal lipid and protein metabolism, an anti-inflammatory effect, improvements of dyslipidemia and endothelial dysfunction, an anti-atherogenic action, and an inhibitory effect on oxidative stress have been reported.[22–24]

Regarding the left ventricular diastolic function in T2DM patients after treatment of pioglitazone, however, divergence emerged. Hence, we tried to reconcile diverse reports and come to a rational conclusion as to how the left ventricular diastolic function varied.

In the process of extracting data, we focused on the left ventricular diastolic function in patients with T2DM after treatment with pioglitazone and other factors as well that may affect it. From the forest plot (Fig. 2), we found that left ventricular diastolic function was improved after pioglitazone treatment. However, high heterogeneity (I^2 = 66%) suggested some confounding factors may have been responsible. Consequently, we performed a subgroup analysis in an attempt to seek the source from which heterogeneity was generated and thus reduce or eliminate the heterogeneity.

In the subgroup analysis, it was assumed that mean age was an important factor, as previous studies had identified this issue but failed to provide an answer.[25,26] Accordingly, the studies were divided into 2 subgroups with an mean age < 55 years and an mean age ≥ 55 years. As shown in Figure 3, left ventricular diastolic function unchanged in T2DM patients whose mean age ≥ 55, but was significantly improved in patients with T2DM with an mean age < 55 years.

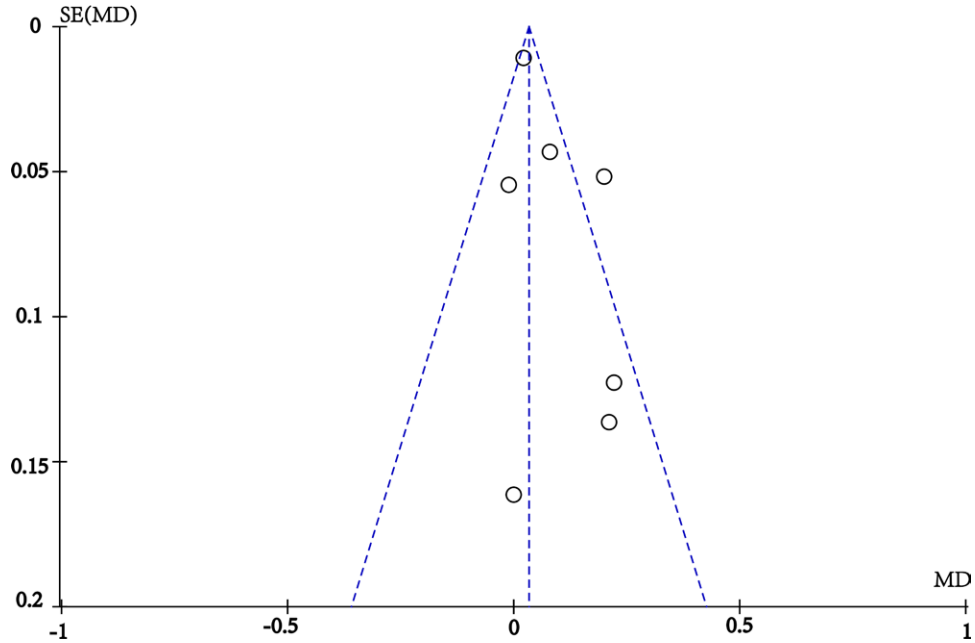

Figure 3. Publication bias was assessed by Funnel plot.

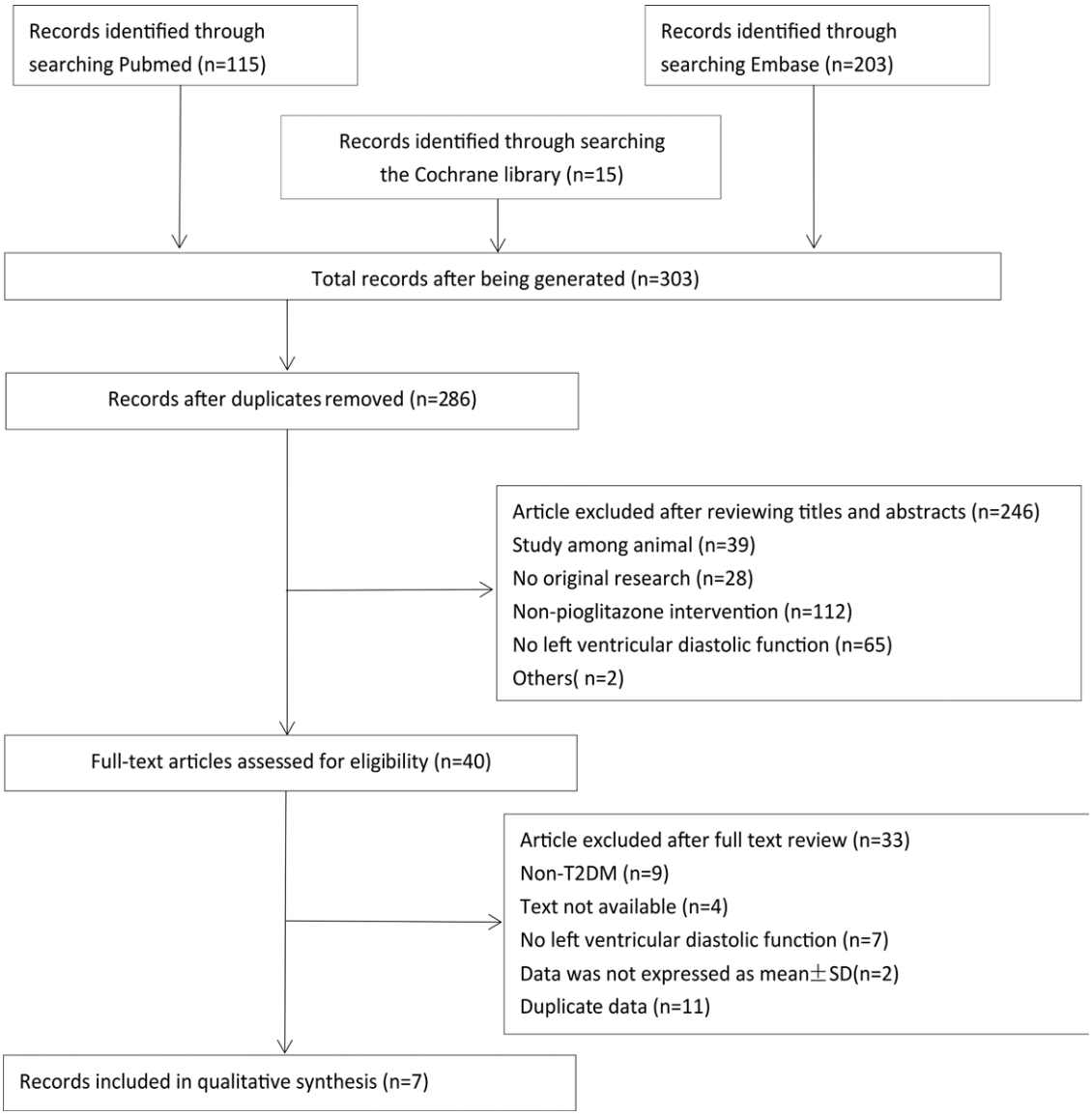

Figure 4. Flowchart of trials selection process.

Table 1

Characteristics of studies included in the meta-analysis.

Reference	Region	Study type	Sample size	Age (yr)	HbA1c(%)	Pre-theraphy (*E/A*)	Post-therapy (*E/A*)	Therapy time	Dosage (mg/d)	Measuring method
Clarke et al 2014[13]	America	Cohort study	12	50.7 ± 9.1	6.8 ± 1.6	1.08 ± 0.3	1.3 ± 0.3	24 w	45	MRI
Clarke et al 2017[11]	America	Cohort study	12	52	6.4 ± 0.4	1.04 ± 0.28	1.25 ± 0.38	24 w	30–45	MRI
Jonker et al 2010[8]	Netherlands	RCT	39	56.8	7.1 ± 0.2	1.07 ± 0.05	1.09 ± 0.05	24 w	30	MRI
Naka et al 2010[7]	Greece	RCT	42	64.3 ± 8.1	8.0 ± 0.9	0.87 ± 0.27	0.86 ± 0.23	24 w	30	Echocardiography
Pala et al 2010[9]	Turkey	RCT	20	55.8	8.4 ± 2.4	1 ± 0.6	1 ± 0.4	16w	30	Echocardiography
Ordu et al 2010[10]	Turkey	Cohort study	49	49	8.59 ± 1.36	0.9 ± 0.23	1.1 ± 0.28	24 w	30	Echocardiography
Terui et al 2006[12]	Japan	Cohort study	15	67.8 ± 12.9	–	0.91 ± 0.23	0.99 ± 0.24	24 w	15–30	Echocardiography

HbA1c = hemoglobin A1c, MRI = magnetic resonance imaging, RCT = randomized controlled trial.

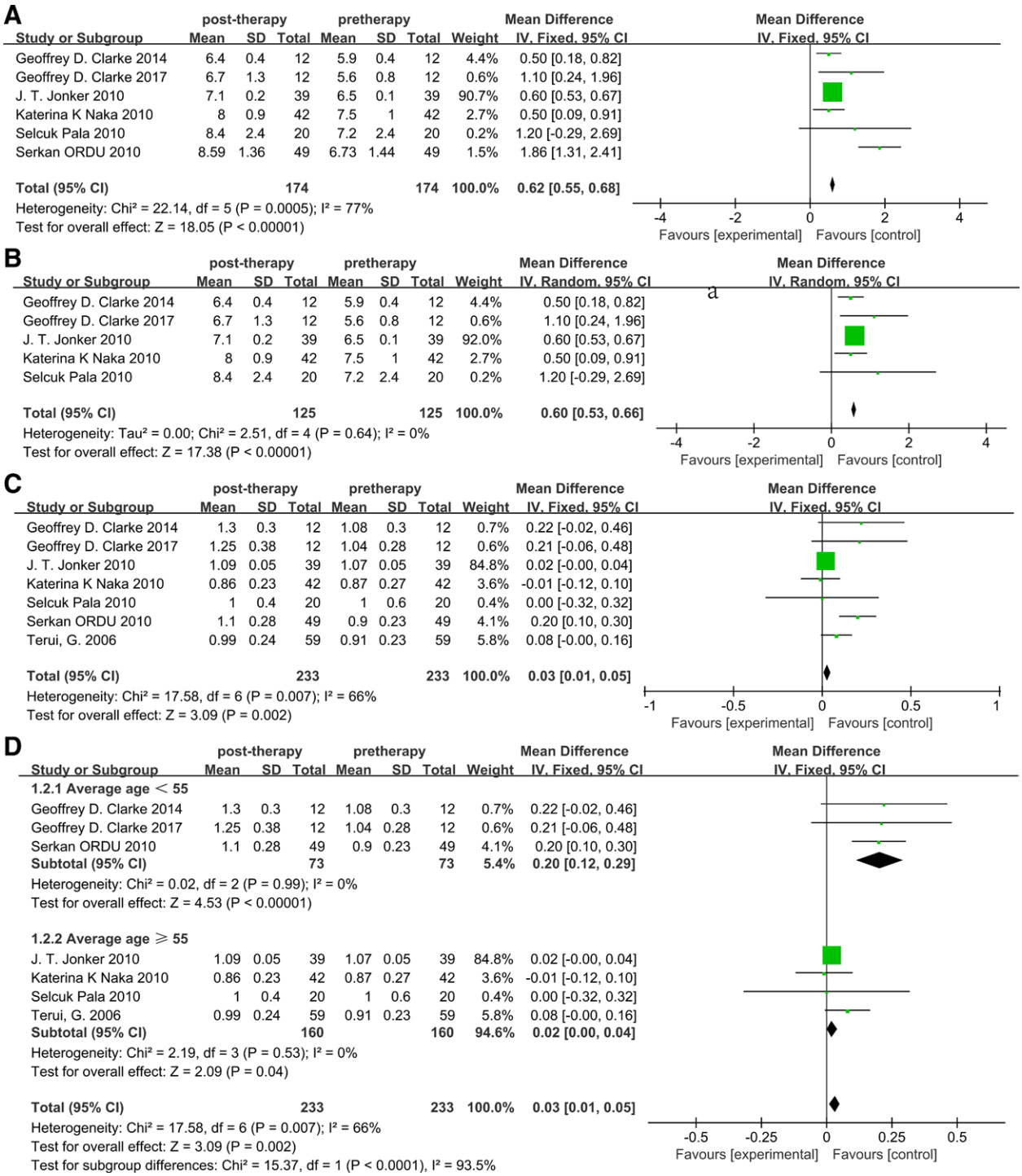

Figure 5. (a) Forest plots show the mean difference in HbA1c (%) change before and after Pioglitazone treatment. (b) After sensitivity analysis, mean difference in HbA1c (%) change before and after Pioglitazone treatment. (c) Forest plots show the mean difference in the value of *E/A* change before and after Pioglitazone treatment. (d) After Subgroup analysis, the mean difference of *E/A* change before and after Pioglitazone treatment. HbA1c = hemoglobin A1c.

Previous data by Hughes et al suggested that improvements in myocardial glucose utilization, lipid metabolism and endothelial function contribute to improved left ventricular performance.[27–29] Several research have found that pioglitazone inhibits myocardial fibrosis, reduces myocardial collagen content and improves left ventricular diastolic function in patients with type 2 diabetes through different pathways.[9,10,30,31] Moreover, Naka et al reported that left ventricular diastolic function in patients was inversely correlated with age and the presence of hypertension, which was similar to previous reports.[26,32] Another study by Clarke et al showed that left ventricular diastolic dysfunction in patients with T2DM was strongly associated with myocardial insulin resistance and glucose metabolism, both of which were improved by pioglitazone.[11] However, the exact mechanism by which left ventricular diastolic function (*E/A*) improves after pioglitazone treatment remains unclear to date.

Based on our current study, we found a significant improvement in left ventricular diastolic function in T2DM patients with a mean age < 55 after treatment with pioglitazone. However, no improvement in left ventricular diastolic function was seen

Table 2

Summary risk estimates of left ventricular diastolic function change after treatment of pioglitazone.

	Number of studies	Fixed effects WMD (95% CI)	I^2 (%)	*P* value
Over all	7	0.03(0.01,0.05)	66	.002
Subgroup analysis				
Study type				
RCT	3	0.02 (–0.00, 0.04)	0	.09
Cohort study	4	0.14 (0.08, 0.20)	24	<.001
Measuring method				
MRI	3	0.02 (0.00, 0.04)	56	.04
Echocardiography	4	0.09 (0.03, 0.14)	63	.001
Dosage				
≤30 mg/d	5	0.03 (0.01, 0.05)	70	.005
>30 mg/d	2	0.03 (0.01, 0.05)	66	.002
HbA1c				
≤7%	2	0.22 (0.04, 0.39)	0	.02
>7%	4	0.03 (0.01, 0.05)	75	.01
Unknown	1	0.08 (–0.00, 0.16)	–	.06

CI = confidence interval, HbA1c = hemoglobin A1c, MRI = magnetic resonance imaging, RCT = randomized controlled trial, WMD = weighted mean difference.

in patients with T2DM with a mean age ≥ 55, suggesting that mean age is an important factor. A plausible model is that pioglitazone improves left ventricular diastolic function in T2DM patients with a mean age < 55 by inhibiting myocardial fibrosis through different pathways. However, in T2DM patients with a mean age ≥ 55 years, myocardial collagen content increases with age and irreversible myocardial fibrosis occurs,[33–35] leading to a decrease in left ventricular diastolic function. The above reasons may limit the potential beneficial effects of pioglitazone on diastolic function.

We also observed and analyzed other factors that may affect left ventricular diastolic function after the treatment of pioglitazone, including pioglitazone dosage (≤30 mg or > 30 mg), HbA1c (7% or ≥ 7%), measurement method (Echocardiography or MRI), study type (RCT or cohort study). However, subgroup analysis did not show a reduction in heterogeneity or the results showed no statistical significance. Therefore, based on the data we have extracted so far, the above factors may not be responsible for explaining the heterogeneity of the overall analysis.

There are limitations in this systematic review and meta-analysis. First, the total number of included studies was only 7 with 233 patients having sufficient data, the potential significance in the overall meta-analysis may not be shown. Second, the duration of pioglitazone treatment for T2DM patients in this meta-analysis was 16 to 24 weeks, the long-term effect needs further study. Additionally, only 3 RCT and 4 cohort study data were searched from the databases and included here, which makes it difficult to evaluate the causal association between left ventricular diastolic function and pioglitazone. Further examination of this possibility requires more evidence-like cohort studies. Therefore, given the above limitations, our results should be interpreted with caution.

5. Conclusion

Pioglitazone significantly improved HbA1c (%) in patients with T2DM, and on the basis of the current evidence, we concluded that patients with T2DM with a mean age < 55 years showed a significant improvement in left ventricular diastolic function after pioglitazone treatment, but in T2DM patients whose mean age ≥ 55 years did not exhibited an improvement in left ventricular diastolic function. Therefore, this treatment option can be considered beneficial for patients with T2DM, especially those young patients with abnormal ventricular diastolic function. Additional clinical trials with larger sample sizes and more available data in different age subgroups may better clarify these issues.

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Writing – review & editing: Yunye Li, Yanwen Bi.

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