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Original Research

Pioglitazone use is associated with reduced risk of Parkinson's disease in patients with diabetes: A systematic review and meta-analysis

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ABSTRACT

Objective: This meta-analysis aimed to evaluate the effect of pioglitazone on Parkinson's disease (PD) in diabetes patients.

Methods: A study search was carried out in PubMed, Embase, and Web of Science databases from inception to July 22, 2021. The Newcastle-Ottawa scale was used to evaluate the quality of the eligible studies. The risk ratio (RR) and 95% confidence intervals (CI) were used as effect size indicators in this meta-analysis to evaluate the risk association between pioglitazone and PD. The Cochran's Q and I^2 tests were used to assess statistical heterogeneity. A dose–response meta-analysis was conducted using the least squares trend estimation method.

Results: Three studies were eligible for this meta-analysis. Compared with diabetes patients who did not use pioglitazone, there was a significant reduction in the risk of PD (RR of 0.87 [95 % CI 0.62–0.99, P = 0.039]) in pioglitazone users. No significant difference in PD risk was noted in diabetes patients taking 438 dose-duration-days (DDDs) of pioglitazone or lower compared with those who did not. When the DDD of pioglitazone was 438, the RR was 0.85 (95 % CI [0.72–1.00], $P = 0.05$). When the DDD of pioglitazone was > 438, the risk of PD in patients with diabetes was significantly decreased ($P < 0.05$) and showed an approximate linear correlation trend.

Conclusion: Pioglitazone administration in PD in diabetes patients is significantly associated with a decrease in the risk of PD.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases in middle-aged and elderly people, mainly due to the depletion of dopamine and the increase of neurotransmitters in the brain [1]. In recent years, the incidence of PD is continue rising, and PD has become one of the major diseases threatening the physical and mental health of middle-aged and elderly people [2]. At present, the specific pathogenesis and etiology of PD are not fully clarified, which may be closely related to various factors, such as genetics, immunity, environment, and apoptosis [3]. In addition, it has been reported that diabetes may be a risk factor for PD. PD and diabetes may have similar pathophysiology [4–6]. Numerous studies have also found an association between diabetes and PD [7–9]. Thus, anti-hyperglycemic agents may have beneficial effects on PD.

The main PD treatment strategy is to administer levodopa (L-dopa) [10], and Deep brain stimulation (DBS) [11], apomorphine [12], Duodopa [13] were the therapeutic strategies for late phase of PD. Pioglitazone is a peroxisome proliferator activated receptor (PPAR) agonist that can improve hyperglycemia and insulin resistance [14,15]. In addition, pioglitazone has also been reported to be a promising drug for the treatment of PD [16,17], and the treatment effect of pioglitazone as a neuroprotective agent for PD has been confirmed in non-human primate and rodent models [18]. However, whether pioglitazone can minimize the risk of PD in patients with diabetes remains controversial. For instance, Chang et al. indicated that pioglitazone could reduce the risk of PD in diabetes patients [19], while Wu et al. did not find a relationship between pioglitazone and PD incidence in diabetes patients [20]. Thus, meta-analysis is needed to analyze the relationship between the use of pioglitazone and the risk of PD in diabetes patients.

In this meta-analysis, the effect of pioglitazone on PD in diabetes patients was evaluated. A recent study also showed that the relationship between pioglitazone and the risk of PD was dose-dependent [19]. Therefore, there might be an association between the dose and

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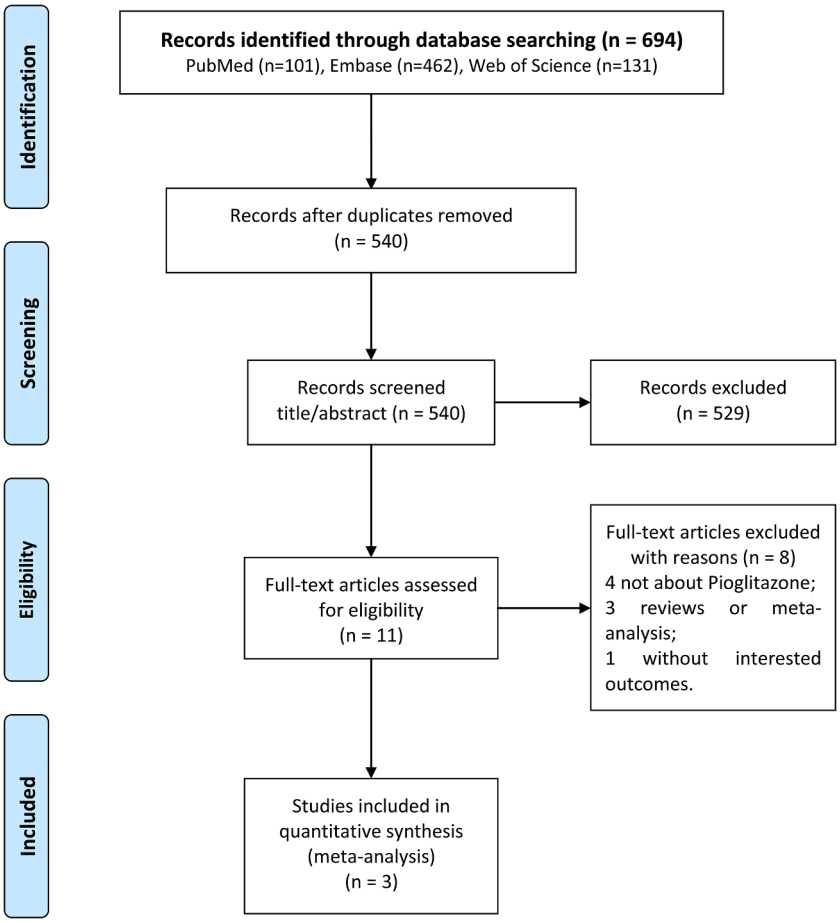

Fig. 1. Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) diagram showing the study screening process.

duration–day (DDD) of pioglitazone and the risk of PD. This study provides a theoretical reference for the effect of pioglitazone on PD in diabetes patients.

2. Materials

2.1. Data sources

From inception to until July 22, 2021, a literature search was carried out in PubMed, Embase, and Web of Science databases with the keywords "Parkinson disease," "pioglitazone," "thiazolidinediones," and "glitazone." The search was performed based on a combination of subject and free words (specific search steps in each database are shown in Supplementary Tables 1–3), without language restrictions. In addition, this study manually searched the literature and screened relevant reviews and references included in the literature.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the literature in this meta-analysis were as follows: 1) the subjects were diabetes patients; 2) observational studies, such as cohort studies and case-control studies; 3) the literature reported a difference in the risk of PD (risk ratio [RR]/hazard ratio [HR] and 95 % confidence intervals [CI]) between pioglitazone users and non-users, or different dose groups of pioglitazone. Meanwhile, studies meeting the following criteria were excluded: 1) reviews, conference abstracts, and comments; 2) diabetes patients taking glitazone, with no independent data on the use of pioglitazone; 3) for repeated literature or the same data reported in multiple studies, only one literature with the most complete study information was extracted, and others were excluded.

2.3. Data extracting and quality evaluation

Two independent researchers participated in data extraction. The available data included first author name, year of publication, study type, study area, study time, basic characteristics of study objects (sample size, age, sex, etc.), study groups (whether patients were administered pioglitazone and pioglitazone dose grouping), confounding factors, and study outcomes. The extraction tables were exchanged after the data extraction was completed by both researchers. Any inconsistencies in the extracted results were resolved by discussion. Furthermore, the Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the study object selection, comparability, and exposure in the included studies [21] (8 scoring items with a full score of 9). A score of 7–9 indicates a high-quality study, 4–6 indicates a medium-quality study, and < 4 indicates a low-quality study.

2.4. Statistical analysis

Stata software (version 12.0) was used for the statistical analysis. The RR and 95 % CI were used as effect size indicators in this analysis to evaluate the risk association between pioglitazone (pioglitazone users vs non-pioglitazone users) and PD. Statistical heterogeneity was assessed using the Cochran's Q test and the I^2 test [22]. Values of $P < 0.05$, $I^2 > 50$ % showed significant heterogeneity, and a random-effects model was applied, whereas $P \geq 0.05$ or $I^2 \leq 50$ % indicated a lack of heterogeneity, and the fixed-effects model was used.

According to the DDD of pioglitazone, the studies were divided into at least three dose groups. The studies could be included in the dose–response meta-analysis if the study met the following criteria: 1) the study showed the HR/RR and 95 % CI of each dose group; 2) the study

Table 1
Characteristics of the included studies.

Study (Area)	Duration	Follow-up, years	Age, years	n, M/F	Group	n	Person-year	Case of PD	HR/RR (95 % CI)	Adjusted factors
Chang, YH 2021 (Taiwan)	1996–2013	mean 6.13	57.91 ± 10.27	48828, 27508/21,320	Non-pioglitazone user	24,414	147006.42	417	1	age, gender, DM duration, insurance range, comorbidities, CCI score, insulin
					Pioglitazone user	24,414	152541.38	275	0.66 (0.57, 0.78)	
					DDDs category					
					0	24,414	147006.42	417	1	
					<453	8151	47102.59	132	1.03 (0.84, 1.26)	
					453–820	8125	49598.14	79	0.58 (0.45, 0.75)	
					>820	8135	55840.65	64	0.43 (0.33, 0.56)	
Wu, HF 2018 (Taiwan)	2002–2008	mean 5	61.15 ± 10.75	15812, 7392/8420	Non-pioglitazone user	7906	39,530	138	1	sex, age, the index year, region, urbanisation level, income, hyperlipidaemia, hypertension, depression, insomnia, head injury, stroke, aspirin, statins and ARB use
					Pioglitazone user	7906	39,530	119	0.90 (0.68, 1.18)	
					DDDs category					
					0	7906	39,530	138	1	
					<365	3949	19,745	64	0.82 (0.59, 1.15)	
					≥365	3957	19,785	55	0.94 (0.66, 1.34)	
Brauer, R 2015 (UK)	1999–2013	5.23 ± 3.75	63.6 (54.4–71.1)	66770, NR/NR	Non-pioglitazone user	51,403	250,996	180	1	age, gender, practice, and treatment stage
					Pioglitazone user	15,367	94,218	57	0.89 (0.65, 1.24)	

ARB, angiotensin receptor blockers; CCI: Deyo-Charlson Comorbidity Index; CI, confidence interval; DDD, dose-duration-day; DM, diabetes mellitus; F, female; M, male; HR, hazard ratio; PD, Parkinson disease; RR, risk ratio; UK, United Kingdom.

reported the number of person-years and PD cases in each dose group. A dose–response meta-analysis was conducted using the least squares trend estimation method reported by Greenland et al. [23] and Orsini et al. [24].

3. Results

3.1. Eligible studies

The detailed screening process of this study is illustrated in Fig. 1. A total of 101, 462, and 131 studies were searched in the PubMed, Embase, and Web of Science databases, respectively. After eliminating duplicate studies, a total of 540 studies were obtained, with 529 studies further excluded as they failed to meet the inclusion criteria after assessing the abstract and title. Among the remaining 11 studies, three relevant studies [19,20,25] were identified after reading the full text. Manual retrieval did not detect any studies that could be included in the current analysis.

3.2. Study characteristics and quality assessments of the eligible studies

The characteristics of eligible studies are illustrated in Table 1. This study included three retrospective cohort studies conducted in Taiwan and the UK with 131,410 participants; the publication years ranged from

Table 2
Quality assessment (the Newcastle-Ottawa Scale) of the included studies.

Study	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Chang, YH 2021	☆	☆	☆	–	☆	☆	☆	☆	7
Wu, HF 2018	☆	☆	☆	–	☆☆	☆	☆	☆	8
Brauer, R 2015	☆	☆	☆	–	☆	☆	☆	☆	7

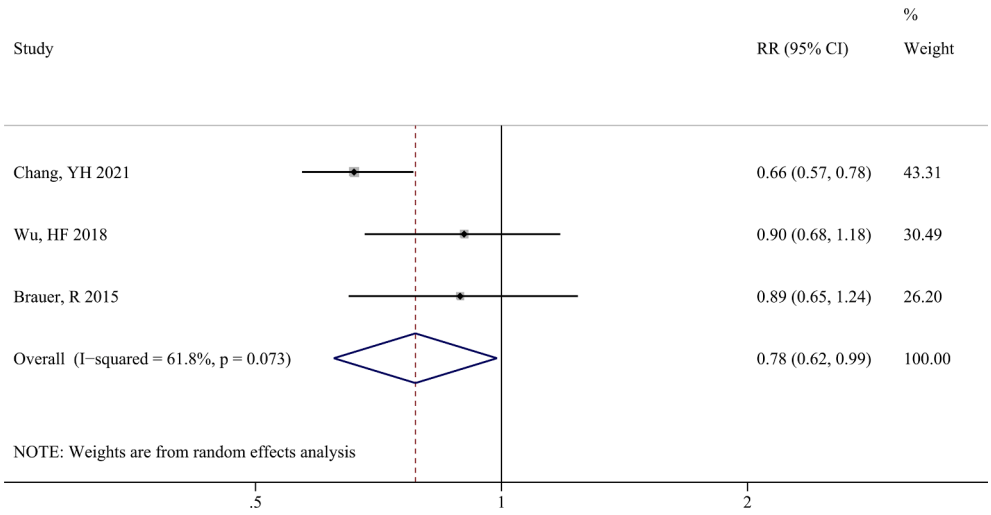

Fig. 2. Forest plot showing the risk association between pioglitazone and Parkinson's disease (PD).

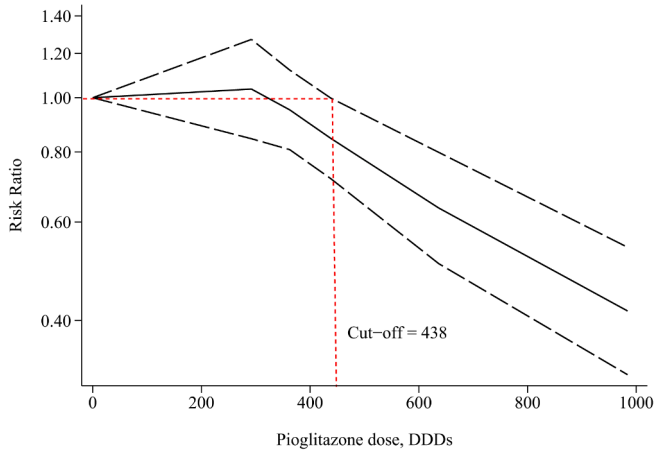

Fig. 3. Forest plot showing the risk association between dose-duration-day (DDD) of pioglitazone and Parkinson's disease (PD).

2015 to 2020. The mean age and follow-up duration of the participants were 57.91–63.60 and 5–6.13 years, respectively. Detailed information on the eligible studies has been illustrated in Table 1. In addition, the NOS score of the eligible studies was 7–8, suggesting that the included studies had relatively high quality (Table 2).

3.3. Results of meta-analysis

All studies [19,20,25] reported a significant risk association between pioglitazone and PD (Fig. 2). The heterogeneity was statistically significant ($I^2 = 61.8$ %, $P = 0.073$), the combined result of RR was 0.78.0 (95 % CI [0.62–0.99]), and the difference between the pioglitazone users and non-users was significant ($P = 0.039$), suggesting that the risk of PD in pioglitazone users in diabetes patients was significantly lower than that in the controls.

3.4. Results of dose–response meta-analysis

Two studies [19,20] reported a risk association between DDD of pioglitazone and PD. First, the risk association between pioglitazone and PD was evaluated using linear correlation hypothesis testing, and the result ($P = 0.010$) was consistent with the nonlinear correlation. The risk association between pioglitazone and PD was evaluated using nonlinear fitting to conduct a dose–response meta-analysis. As shown in Fig. 3, with the increase in pioglitazone intake days, the risk of PD first increased and then decreased. However, the difference between the risk of PD in diabetes patients taking 438 DDDs of pioglitazone or lower and in those not taking pioglitazone was not significant. When the DDD of pioglitazone was 438, the RR was 0.85 (95 % CI [0.72–1.00], $P = 0.05$). When the DDD of pioglitazone was>438, the risk of PD in patients with diabetes was significantly decreased ($P < 0.05$) and showed an approximate linear correlation trend.

4. Discussion

Herein, the results showed that pioglitazone administration in PD in diabetes patients is significantly associated with a decrease in the risk of PD, but this beneficial effect was also dose-dependent. As this meta-analysis was conducted on a large sample size, the results were accurate and reliable. Additionally, the methodology of the included studies was of high quality, and the control of selection bias and hybrid bias was reasonable. Moreover, to the best of our knowledge, this is the first meta-analysis to analyze the effect of pioglitazone on PD in diabetes patients.

Numerous studies have investigated the relationship between pioglitazone and PD due to pioglitazone's neuroprotective effects and its ability to restrain inflammatory responses. Liu et al. found that pioglitazone can reduce neuroinflammation in the nigrostriatal system and improve the survival of dopaminergic neurons after diffuse brain injury in rats [26]. In mouse models of PD, pioglitazone has been shown to be an effective neuroprotectant [18]. However, it has been reported that diabetes patients are at risk for PD, and diabetes can facilitate the incidence of PD [4,5]. Moreover, the relationship between pioglitazone and the risk of PD in diabetes patients remains controversial. This meta-analysis found that pioglitazone administration in PD in diabetes patients is significantly associated with a decrease in the risk of PD. The results of the meta-analysis were in accordance with those of other studies. Chang et al. revealed that pioglitazone is a potential drug for minimizing the incidence of PD in diabetes patients [19]. Brauer et al. have illustrated that pioglitazone is responsible for reduction in the incidence of PD, and PPAR gamma pathways may be a fruitful drug target in PD [25]. In addition, a previous study found that PPAR pathways play important roles in the pathogenesis of PD [27]. However, the mechanisms underlying the effect of pioglitazone on PD in diabetes patients should be further investigated.

Moreover, some reports indicated that pioglitazone could not minimize the risk of PD, which needs to be further discussed. For instance, Connolly et al. found that pioglitazone was not related to a longer duration of PD diagnosis [28]. Wu et al. showed that pioglitazone may not minimize the risk of PD with diabetes [20]. However, these results

may be due to several inherent limitations, such as follow-up duration and ethnicity variance, because PD is a multifactorial disease, which may be affected by ethnic, genetic, and environmental factors. In addition, PD is a progressive disease, and these results may be affected by insufficient exposure to pioglitazone [29]. This meta-analysis indicated that only > 438 DDDs of pioglitazone would be beneficial. In combination with other studies showing the risk of pioglitazone for PD [30,31], this study may provide a clearer view of the impact of pioglitazone on the risk of PD in diabetes patients.

There are some limitations in this study. First, most of the indicators have been included in a few studies; therefore, we were unable to analyze the source of heterogeneity through subgroup analysis, meta-regression, and other quantitative methods. Second, all the included studies were retrospective cohort studies, although multivariate analyses were conducted to correct the effects of confounding factors on the results, the inconsistency of the corrected factors would also bring heterogeneity to the results. Third, only three studies were eligible for this meta-analysis, and the efficacy of either the Egger's test or the qualitative method was relatively low; therefore, publication bias tests were not performed in this meta-analysis. Finally, the studies included in this study did not report the reaction of PD drug treatment, whether the PD exists in the family history, gene mutation and other information, and it was uncertain whether these features have been included in the correction factors, which should be further explored.

5. Conclusion

In summary, our meta-analysis results indicated that pioglitazone administration in PD in diabetes patients is significantly associated with a decrease in the risk of PD. More high-quality studies may be worthwhile to confirm the treatment effect of pioglitazone on PD prevention. This study provides new insights into the effects of pioglitazone on the risk of PD in diabetes patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The data and materials used in this study are available from the corresponding authors upon request.

Authors' Contributions

Liudan Chen drafted the manuscript. Yangu Tao carried out the literature search, data acquisition, data analysis and manuscript preparation. Jianjun Li and Mengru Kang performed concepts design and confirmed the authenticity of the raw data. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2022.10.023.

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