

Effectiveness and safety of different doses of pioglitazone in psoriasis: a meta-analysis of randomized controlled trials

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Abstract

Background: Pioglitazone may be beneficial in the treatment of psoriasis. However, based on the effectiveness and safety considerations, it has not been widely used. To fully evaluate the strength of evidence supporting psoriasis treatment with pioglitazone, we conducted a meta-analysis of existing published studies.

Methods: PubMed, Ovid, Cochrane Library, Google Scholar, and Web of Science databases were systematically searched before February 2019. Randomized controlled trials (RCTs) of pioglitazone administration compared with placebo, administered to patients with psoriasis for at least 10 weeks, and published in English were included. Quality of the included RCTs was identified by the modified Jadad scale. The quality of evidence for each outcome was evaluated using the GRADEpro Guideline Development Tool online software. Primary outcomes were proportion of patients showing psoriasis area and severity index (PASI) score improvement (>75%) and the mean percent change in PASI score from baseline to the end of treatment. Dichotomous data were analyzed using odds ratios (ORs) corresponding to the 95% confidence interval (CI), whereas continuous variables, expressed as mean and standard deviation, were analyzed using the mean differences (MD) with the 95% CI.

Results: Six RCTs were analyzed. Meta-analysis showed that pioglitazone reduced the PASI scores in patients with psoriasis compared with the control group when administered at 30 mg per day ($P < 0.001$, MD = -3.82, 95% CI = -5.70, -1.93) and at 15 mg per day ($P = 0.04$, MD = -3.53, 95% CI = -6.86, -0.20). The PASI-75 of the pioglitazone group was significantly higher than that of the control group at 30 mg per day ($P < 0.001$, OR = 8.30, 95% CI = 3.99, 17.27) and at 15 mg per day ($P = 0.03$, OR = 2.96, 95% CI = 1.08, 8.06). No statistically significant differences in total adverse events were observed between the groups. There were no significant differences in common adverse reactions such as weight gain and elevated liver enzymes between the two pioglitazone groups.

Conclusions: Use of pioglitazone in the current treatment of psoriasis is beneficial. The therapeutic effect of the daily 30 mg dose may be greater than that of the 15 mg dose per day with no significant change in the frequency of adverse reactions.

Keywords: Meta-analysis; Psoriasis; Pioglitazone

Introduction

Psoriasis is a clinically common chronic inflammatory skin disease characterized by erythematous scales and affecting 2% to 4% of the global population.^[1] Its pathogenesis is still unclear, and it is generally believed to be the result of a combination of genetic and environmental factors, that is, a genetic propensity to immune dysfunction in the presence of a variety of factors such as infections, drugs, diet, and metabolic disorders.^[2-5] The combined effects of these factors ultimately lead to hyperproliferation of skin keratinocytes, abnormal apoptosis, and abnormal regeneration of dermal endothelial cells in the dermal papillae, resulting in the characteristic lesions of psoriasis. Psoriasis often recurs and can lead to an increased risk of other

systemic diseases, seriously affecting the quality of life of the patients.^[6] Traditional psoriasis treatments include methotrexate, acitretin, cyclosporine, and photochemotherapy, but there are risks of liver and kidney toxicity, carcinogenesis, and teratogenesis with long-term use, which limits their clinical application.

Thiazolidinediones (TZDs) are anti-diabetic drugs that can activate nuclear peroxisome proliferator-activated receptor (PPAR)- γ agonists, thereby improving the body's sensitivity to insulin and reducing hepatic gluconeogenesis.^[7] Currently, TZDs are mainly used in the clinical treatment of type 2 diabetes. PPARs are expressed in many cell types and are expressed primarily in epidermal keratinocytes of the skin. Activation of these receptors

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DOI:
10.1097/CM9.0000000000000642

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Chinese Medical Journal 2020;133(4)

Received: 14-08-2019 Edited by: Yuan-Yuan Ji

can inhibit the proliferation of keratinocytes in patients with psoriasis.^[8] TZDs also have anti-cell proliferation and anti-inflammatory effects.^[9,10] Therefore, they may have potential therapeutic effects on psoriasis.

In 2012, Malhorta *et al*^[11] reviewed TZDs and psoriasis. They concluded that pioglitazone appeared to show effectiveness in the treatment of psoriasis. However, only two studies were reviewed in their paper, which provided insufficient evidence for the drug in the treatment of psoriasis. At present, a number of clinical randomized controlled trials (RCTs) have focused on the effectiveness and safety of pioglitazone in psoriasis treatment. To provide further evidence in the treatment of psoriasis with pioglitazone, we conducted a meta-analysis of the existing published studies.

Methods

Literature search

Databases of the Cochrane Library, PubMed, Ovid, Google Scholar, and Web of Science were systematically searched. These computer searches were limited to articles published in English before February 2019, excluding editorials and reviews. The following keywords were used for the search: “pioglitazone” OR “thiazolidinedione” OR “TZD” AND “psoriasis.” Additional published data that met our inclusion criteria were identified by reviewing the bibliographical references listed in the retrieved articles.

We included studies that met the following criteria: (1) all RCTs of pioglitazone administered to patients with psoriasis for at least 10 weeks; (2) trials in which local anti-psoriatic treatment or systemic treatment including methotrexate and acitretin were included; and (3) studies that presented data as the mean percent change in the psoriasis area and severity index (PASI) score^[12] from baseline to the end of the treatment and/or data on the proportion of patients showing PASI score improvement (>75%).

Studies were excluded from the analysis if (1) they were non-published studies or publications that lacked original data for the meta-analysis; and (2) they contained duplicate data.

This meta-analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines. The protocol for the meta-analysis is available in the international prospective register of systematic reviews (PROSPERO) with the registration number CRD 42018106413.

Data extraction

The data were independently extracted from all the included studies by two authors (Zhang JZ and Ding Y). Disagreement was resolved by consensus. If consensus could not be reached, the results were reviewed by a third author (Kang XJ). The extracted data included the following items: first author, publication year, psoriasis typing, study area, sample size, age of patients, PASI-75, treatment strategy, and the modified Jadad score.

Assessment of the quality of identified studies

The Cochrane Collaboration tool was used for assessing risk of bias.^[13] The quality of the included RCTs was identified using the modified Jadad scale, which included the following domains: randomization, blinding, and patient attrition.^[14] The modified Jadad scale scores range from 0 to 7. Studies with a score equal to or higher than 4 were considered to be of high quality. Two investigators (Yu SR and Ding Y) independently assessed the risk of bias and the quality of the included studies, and the results were reviewed by a third investigator (Xiang F). Disagreement was resolved by consensus.

Statistical analysis

The reduction in disease severity was assessed based on changes in lesion reduction. The PASI score was used in clinical trials to measure the outcome of psoriasis treatment. The PASI measures the redness, thickness, scaling of the lesion and the involved area, with a total score ranging from 0 to 72. PASI-75 has been adopted as a standard treatment goal by a European expert consensus group,^[15] which refers to a 75% reduction in PASI and is considered as successful treatment of psoriasis.

The outcome measures were both dichotomous (PASI-75) and continuous (change in PASI score) between the pioglitazone groups and the control groups. Dichotomous data were analyzed using odds ratios (ORs) corresponding to the 95% confidence interval (CI), whereas continuous variables, which were expressed as the mean \pm standard deviation, were analyzed using the mean differences (MD) with the 95% CI. Heterogeneity between studies was assessed by the I^2 statistic and $P < 0.10$, and $I^2 > 50\%$ indicated evidence of heterogeneity.^[16,17] If heterogeneity existed among the studies, the random-effects model was used.^[18] Otherwise, the fixed-effects model was adopted.^[19] Sensitivity analyses were performed by the single exclusion of one study to assess the heterogeneity and robustness of the pooled results. Publication bias was directly judged by the funnel plot. The difference was statistically significant at $P < 0.05$. Analyses were performed using RevMan 5.33 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Evidence quality evaluation

The quality of evidence for each outcome was evaluated using the GRADEpro Guideline Development Tool online software (GRADEpro GDT), which evaluates using five primary domains (risk of bias, inconsistency, indirectness, imprecision, and other considerations) and is divided into four levels (high, moderate, low, and very low).

Results

A total of 193 articles were retrieved. After duplicates were removed, 117 full-text studies were evaluated. With further screening, six clinical studies were eventually included in the final meta-analysis.^[20-25] In four studies,^[20-22,25] the dose of pioglitazone in the pioglitazone group was 30 mg per day. In one study,^[23] the dose of pioglitazone was 15 mg per day. In another study,^[24] the dose of pioglitazone was either 15 mg

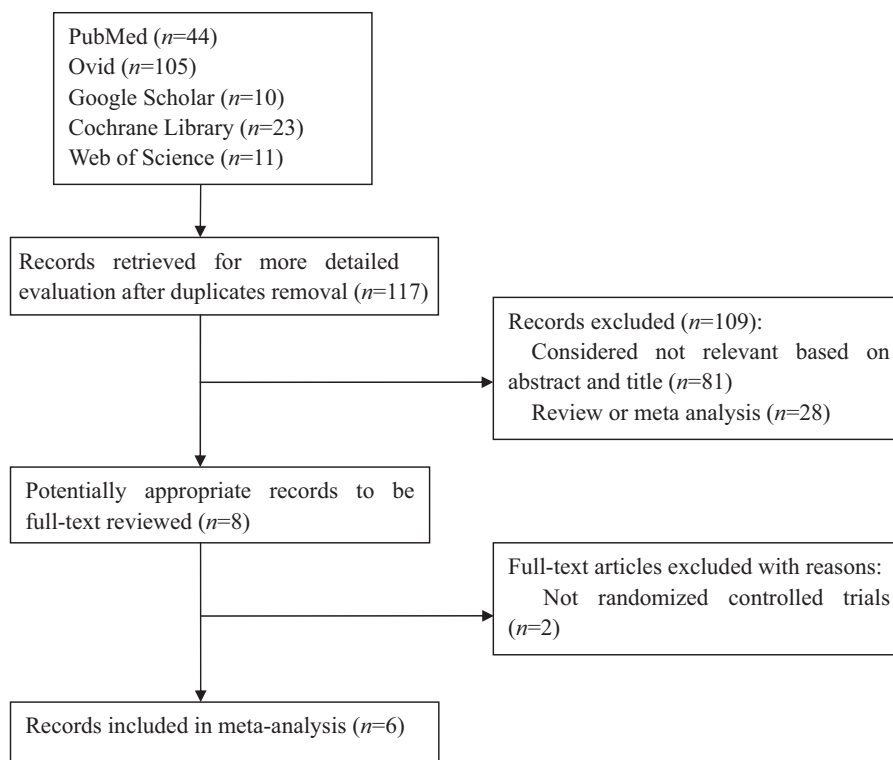


Figure 1: Flow diagram of the study identification.

Table 1: Characteristics of included six randomized controlled trials of pioglitazone administration compared with placebo.

First author	Years	Psoriasis typing	Study area	Sample size		Age (years)		PASI-75		Treatment strategy		Modified Jadad scale
				Pioglitazone	Control	Pioglitazone	Control	Pioglitazone	Control	Pioglitazone	Control	
Ghiasi <i>et al</i>	2019	Plaque	Iran	30	30	42.8 ± 15.0	44.0 ± 16.9	24	12	30 mg/day, 10 weeks, NB-UVB	Placebo, NB-UVB	5
Hafez <i>et al</i>	2015	PV	Egypt	24	24	39.6 ± 13.9	44.5 ± 12.8	5	1	30 mg/day, 10 weeks	Placebo	6
Lajevardi <i>et al</i>	2015	Plaque	Iran	22	22	36.2 ± 12.8	42.5 ± 16.1	4	0	30 mg/day, 16 weeks, MTX	Placebo, MTX	5
Mittal <i>et al</i>	2009	Plaque	India	19	22	42.2 ± 10.6	38.1 ± 11.5	8	5	15 mg/day, 12 weeks, Acitretin	Placebo, Acitretin	5
Shafiq <i>et al</i> (a)	2005	Plaque	India	21	25	33.2 ± 11.2	34.6 ± 10.3	7	3	15 mg/day, 10 weeks	Placebo	5
Shafiq <i>et al</i> (b)	2005	Plaque	India	24	25	36.9 ± 11.9	34.6 ± 10.3	9	3	30 mg/day, 10 weeks	Placebo	5
Singh <i>et al</i>	2016	N/A	India	16	23	44.0 ± 12.9	46.9 ± 10.4	13	1	30 mg/day, 12 weeks	Placebo	4

PASI: Psoriasis area and severity index; N/A: Not applicable; PV: Psoriasis vulgaris; NB-UVB: Narrow bound ultra violet B light; MTX: Methotrexate.

or 30 mg per day. The observation time of the studies ranged from 10 to 16 weeks. Figure 1 shows the process of literature retrieval. Table 1 shows the studies identified and their main characteristics. Regarding the quality of the included studies in our meta-analysis, the modified Jadad scale scores of the studies were ≥4 (high quality).

Risk bias assessment of included studies

All the six eligible studies were randomized trials and almost all were double-blind.^[20,21,23-25] Three of the studies specified the method of randomization,^[21,23,25] while two included a description of the blinding method.^[21,23] Figure 2 shows the risk bias assessment of the studies.

Effectiveness of pioglitazone

All pioglitazone treatments significantly reduced the PASI score from baseline to the end of the treatment.^[20-25] There

was significant heterogeneity among the studies and in the different sub-groups; therefore, the data were combined using random-effects models. Meta-analysis showed that pioglitazone could reduce the PASI score in patients with psoriasis when compared with the control group in both the 30 mg group ($P < 0.001$, MD = -3.82, 95% CI = -5.70, -1.93) and the 15 mg group ($P = 0.04$, MD = -3.53, 95% CI = -6.86, -0.20). There was no statistically significant difference between the two pioglitazone sub-groups ($P = 0.89$, $I^2 = 0$) [Figure 3].

Five studies^[20-23,25] provided PASI-75 of pioglitazone for psoriasis. The PASI-75 data of Shafiq *et al*^[24] were obtained from other studies.^[26] We performed sub-group analysis according to the different doses of pioglitazone. There was no significant heterogeneity among the studies and the different sub-groups; therefore, the data were combined using a fixed-effects model. Meta-analysis

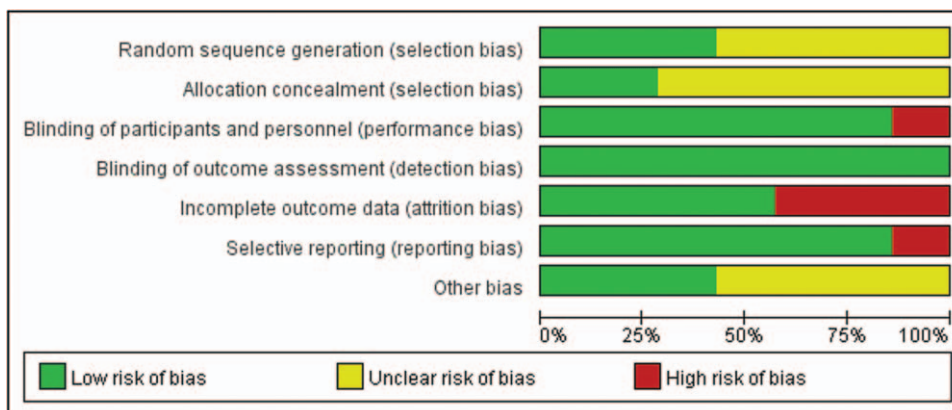


Figure 2: Risk of bias graph (authors' judgment about each risk of bias item presented as percentages across all included studies).

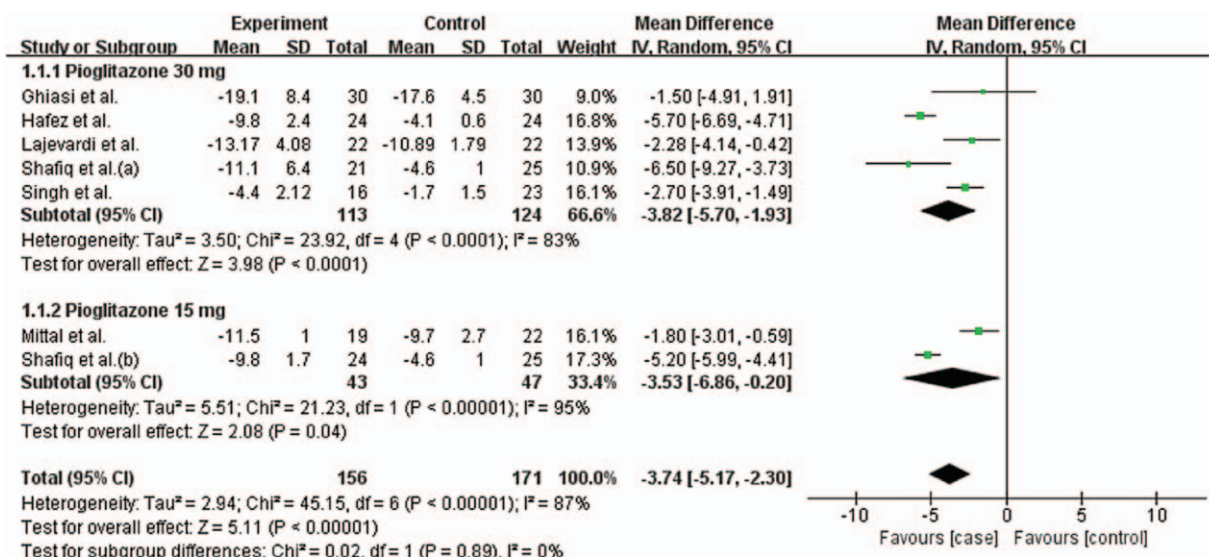


Figure 3: Forest plot of change in PASI score in the pioglitazone trials compared to placebo (sub-group: 30 or 15 mg per day). PASI: Psoriasis area and severity index.

showed that the treatment efficiency of the pioglitazone group was significantly higher than that of the control group at 30 mg per day ($P < 0.001$, OR = 8.30, 95% CI = 3.99, 17.27) and at 15 mg per day ($P = 0.03$, OR = 2.96, 95% CI = 1.08, 8.06). There was no statistically significant difference between the two pioglitazone sub-groups ($P = 0.10$, $I^2 = 62.3\%$). The results are shown in Figure 4.

Safety of pioglitazone

In a safety study of pioglitazone, two studies compared the total adverse events in the pioglitazone group and the control group. No statistically significant differences in adverse events were found between the 30 mg group ($P = 0.54$, OR = 1.46, 95% CI = 0.44, 4.88) or the 15 mg group ($P = 0.44$, OR = 1.75, 95% CI = 0.42, 7.25) when compared with the control group. Except for one study^[23] that reported a myocardial infarction in the control group, no serious adverse events, including hypoglycemia events, were reported in the other studies. In addition, there were no significant differences in the occurrence of common

adverse events, including weight gain and elevated liver enzymes between the pioglitazone group and the control group. We also performed sub-group analyses based on different doses. Four studies^[22-25] reported weight gain after treatment. However, this finding was not statistically significant ($P = 0.25$, OR = 2.03, 95% CI = 0.61, 6.77 for the 30 mg group and $P = 0.78$, OR = 1.20, 95% CI = 0.32, 4.45 for the 15 mg group). Three studies^[22,24,25] reported elevated liver enzymes after treatment. This was also not statistically significant for the 30 mg group ($P = 0.32$, OR = 3.20, 95% CI = 0.32, 31.87) and the 15 mg group ($P = 0.43$, OR = 3.73, 95% CI = 0.14, 96.53).

Sensitivity analysis and publication bias

Sensitivity analysis was performed on both the effectiveness and safety endpoints. The results showed that the combined effects were not affected by a single study except that Shafiq *et al*^[24] had an undue influence on the summary ORs of PASI-75 in the 15 mg group. After exclusion of this study, the P -value of the daily oral 15 mg pioglitazone treatment group became statistically insignificant

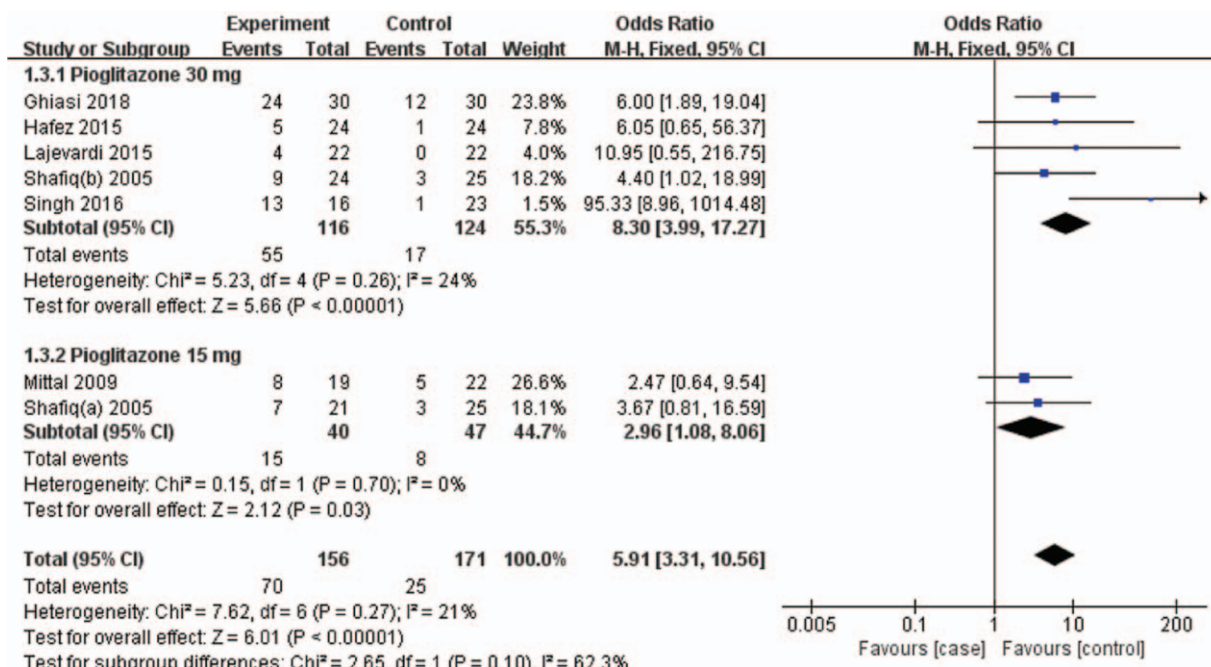


Figure 4: Forest plot of PASI-75 in the pioglitazone trials compared to placebo (sub-group: 30 or 15 mg per day). PASI: Psoriasis area and severity index.

(P = 0.13). In terms of publication bias, the funnel plots of the change in PASI score and PASI-75 in the pioglitazone trials compared to placebo showed a significant asymmetry, which indicated an obvious publication bias. We did not conduct a publication bias test for studies with small sample sizes.

Evidence quality evaluation

We used the GRADEpro GDT to evaluate the quality of evidence for the following primary outcomes: change in PASI score, PASI-75, elevated liver enzymes, weight gain, and total adverse events. The results suggested that the quality of the evidence in the PASI-75 and elevated liver enzymes were high, while the quality of the evidence for the change in PASI score, weight gain, and total adverse events was intermediate [Table 2].

Discussion

Psoriasis is a clinically common dermatological disease, the symptoms and related complications of which seriously affect the quality of life in patients.^[27,28] The treatment of psoriasis has also been a hot spot for psoriasis patients and dermatologists. For patients with moderate or severe psoriasis, systematic treatment should be provided. The commonly used drugs are cyclosporine, methotrexate, acitretin, *Tripterygium wilfordii* polyglycoside tablets, apremilast, and various biological agents.^[29-32] The prevalence of diabetes mellitus is increasing in patients with psoriasis^[33-35] and insulin resistance plays a role in the pathogenesis of psoriasis.^[36-38]

It has been reported that the use of hypoglycemic drugs, such as dipeptidyl peptidase-4 inhibitors, biguanides,

TZDs, and glucagon-like peptide-1 receptor agonists, can improve the symptoms of psoriasis.^[39-42] Chang *et al*^[26] analyzed the effect of pioglitazone in the treatment of plaque psoriasis. However, they did not evaluate the efficacy and safety of the drug at different doses. In this study, the data of six randomized controlled trials were summarized by meta-analysis. The results showed that pioglitazone can significantly reduce the PASI score of patients with psoriasis and improve the treatment effectiveness. In terms of drug safety in patients with psoriasis, there were no significant adverse events.

We performed a sub-group analysis of different doses of pioglitazone in this study and found that the percentage reduction in the mean PASI score for the 30 mg group was higher than that of the 15 mg group. This translates to a dose-dependent improvement in psoriasis. Shafiq *et al*^[24] conducted an RCT in 2005 in which patients were divided into the three following groups: a placebo, 15 mg per day pioglitazone, and 30 mg per day pioglitazone. The percentage reduction in the mean PASI scores for the placebo, and pioglitazone 15 mg and 30 mg groups were 21.6%, 41.1%, and 47.5%, respectively. This is consistent with our findings.

TZDs were originally used in patients with type 2 diabetes in the late 1990s. These drugs are ligands for PPARs, which are ligand-activated receptors in the nuclear hormone receptor family and expressed in many cell types. PPARs are also present in the skin, mainly in the sebaceous glands, epidermis, inner root sheath, and fat cells. There are three sub-types that control many intracellular metabolic processes. Vitamin D3, retinoic acid, thyroid hormone receptors, and steroids are also members of this superfamily.^[43] Anti-psoriatic drugs, including acitretin, calcipotriol, and corticosteroids, act through these receptors. To a

Table 2: Evaluation of GRADEpro GDT in patients with psoriasis treated by pioglitazone or placebo.

Items	Certainty assessment						No of patients		Effect		Quality of the evidence (GRADE)	Comments		
	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Pioglitazone	Placebo			Relative (95% CI)	Absolute (95% CI)
							Publication bias strongly suspected [‡]	response gradient						
Change in PASI score	7	Randomized trials	Not serious	Not serious	Serious*	Not serious	Publication bias strongly suspected [‡]	156	171	-	MD 3.74 lower (5.17 lower to 2.3 lower)	⊕⊕⊕⊕ MODERATE	CRITICAL	
PASI-75	7	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [‡]	70/156 (44.9%)	25/171 (14.6%)	OR 5.91 (3.31–10.56)	357 more per 1000 (from 216 more to 498 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
Elevated liver enzymes	4	Randomized trials	Not serious	Not serious	Not serious	Serious [†]	Strong association	3/83 (3.6%)	0/95 (0)	OR 3.37 (0.51–22.01)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	
Weight gain	5	Randomized trials	Not serious	Not serious	Not serious	Serious [†]	None	14/102 (13.7%)	13/117 (11.1%)	OR 1.60 (0.66–3.86)	56 more per 1000 (from 35 fewer to 214 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT	
Total adverse events	2	Randomized trials	Not serious	Not serious	Not serious	Serious [†]	None	25/41 (61.0%)	23/44 (52.3%)	OR 1.58 (0.63–3.95)	111 more per 1000 (from 114 fewer to 290 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT	

* Mean or mean percent change in PASI from baseline to end of treatment with pioglitazone or placebo were calculated from the relevant data in the articles,^[20-24] reference Malhotra *et al.*^[11] One of the studies data was obtained by contacting authors^[25]; [†]Limited sample size; [‡]Funnel plot showed significant asymmetry. Although the publication bias test of small sample size studies is still controversial. GRADE Working Group grades of evidence: High quality, further research is very unlikely to change our confidence in the estimate of effect; Moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate. CI: Confidence interval; PASI: Psoriasis area and severity index; OR: Odds ratio; MD: Mean difference. ⊕: Evidence quality symbol. ⊕: Downgraded one level.

certain extent, this explains the therapeutic effects of TZDs on psoriasis.

TZDs such as pioglitazone can inhibit excessive proliferation of skin keratinocytes, increase expression of differentiation markers such as epithelin and intermediate filament-associated proteins, and thus promote differentiation of keratinocytes.^[44] In patients with psoriasis, pioglitazone can reduce the infiltration of inflammatory cells into the skin and reduce the expression of inflammatory factors, such as interleukin 2 and C-reactive protein, and thus exert an inhibitory effect on the local immune inflammatory response.^[45] In addition, TZDs can also inhibit the formation of new blood vessels.^[46] The beneficial effect of pioglitazone seen in the treatment of psoriasis may be exerted via the above pathophysiological mechanisms.

Previous studies have confirmed that pioglitazone has better overall safety in the treatment of patients with diabetes. It does not increase the risk of cardiovascular events, though rosiglitazone, which is also a TZD, may increase this risk.^[47,48] A review by Lee *et al.*^[49] suggests that pioglitazone may even reduce the risk of myocardial infarction and stroke. Another TZD, troglitazone, was removed from the market due to severe liver toxicity.^[50] However, this study did not find any serious adverse events associated with pioglitazone, and the drug did not increase the incidence of common adverse events, indicating that the drug is safe for patients with psoriasis.

The study had some limitations. There was significant heterogeneity in the pooled analysis of reduced PASI scores, which could not be explained in the sub-group analysis based on different doses. The existence of clinical heterogeneity may lead to a statistical heterogeneity of results to some extent. The heterogeneity may be related to the duration of medication, the differences in the combination therapy, accompanying diseases, subjects' gender and age, as well as other potential factors. Sub-group analyses were limited due to the small sample size of some of the included studies. Furthermore, most of the included studies were short-lived and the long-term efficacy and safety of pioglitazone on psoriasis could not be determined.

These results provide a reference for the application of pioglitazone in patients with psoriasis, especially in psoriasis patients with diabetes mellitus. Pioglitazone is an effective and safe option in the treatment of patients with psoriasis. The therapeutic response is dose-dependent. More large-scale and long-term follow-up clinical trials are needed to further confirm the findings of this study.

Conflicts of interest

None.

References

- Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated Comorbidity (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013;133:377–385. doi: 10.1038/jid.2012.339.
- Wang WM, Jin HZ. Skin microbiome: an actor in the pathogenesis of psoriasis. *Chin Med J* 2018;131:95–98. doi: 10.4103/0366-6999.221269.
- Bhatia BK, Millsop JW, Debbaneh M, Koo J, Linos E, Liao W. Diet and psoriasis, part II: celiac disease and role of a gluten-free diet. *J Am Acad Dermatol* 2014;71:350–358. doi: 10.1016/j.jaad.2014.03.017.
- Di Meglio P, Duarte JH, Ahlfors H, Owens ND, Li Y, Villanova F, *et al.* Activation of the aryl hydrocarbon receptor dampens the severity of inflammatory skin conditions. *Immunity* 2014;40:989–1001. doi: 10.1016/j.immuni.2014.04.019.
- Wang WM, Wang KY, Wang T, Jin HZ, Fang K. Hydroxychloroquine-induced psoriasis-form erythroderma in a patient with systemic lupus erythematosus. *Chin Med J* 2018;131:1887–1888. doi: 10.4103/0366-6999.237411.
- Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, *et al.* Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol* 2017;76:377–390. doi: 10.1016/j.jaad.2016.07.064.
- Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004;351:1106–1118. doi: 10.1056/NEJMra041001.
- Ellis CN, Varani J, Fisher GJ, Zeigler ME, Pershadsingh HA, Benson SC, *et al.* Troglitazone improves psoriasis and normalizes models of proliferative skin disease: ligands for peroxisome proliferator-activated receptor-gamma inhibit keratinocyte proliferation. *Arch Dermatol* 2000;136:609–616. doi: 10.1001/archderm.136.5.609.
- Morikang E, Benson SC, Kurtz TW, Pershadsingh HA. Effects of thiazolidinediones on growth and differentiation of human aorta and coronary myocytes. *Am J Hypertens* 1997;10:440–446. doi: 10.1016/S0895-7061(97)90528-8.
- Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature* 1998;391:79–82. doi: 10.1038/34178.
- Malhotra A, Shafiq N, Rajagopalan S, Dogra S, Malhotra S. Thiazolidinediones for plaque psoriasis: a systematic review and meta-analysis. *Evid Based Med* 2012;17:171–176. doi: 10.1136/ebmed-2011-100388.
- Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. *Dermatologica* 1978;157:238–244. doi: 10.1159/000250839.
- Higgins JPT, Green S (eds) *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org. [Accessed on December 10, 2016]
- Oremus M, Wolfson C, Perrault A, Demers L, Momoli F, Moride Y. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. *Dement Geriatr Cogn Disord* 2001;12:232–236. doi: 10.1159/000051263.
- Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011;303:1–10. doi: 10.1007/s00403-010-1080-1.
- Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. *PLoS One* 2007;2:e841. doi: 10.1371/journal.pone.0000841.
- Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med* 1995;14:395–411. doi: 10.1002/sim.4780140406.
- DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 2007;28:105–114. doi: 10.1016/j.cct.2006.04.004.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–748. doi: 10.1016/0021-9681(79)90031-6.
- Ghiasi M, Ebrahimi S, Lajevardi V, Taraz M, Azizpour A. Efficacy and safety of pioglitazone plus phototherapy versus phototherapy in patients with plaque type psoriasis: a double blinded randomized controlled trial. *J Dermatolog Treat* 2019;30:664–667. doi: 10.1080/09546634.2018.1544702.
- Hafez VG, Bosseila M, Abdel Halim MR, Shaker OG, Kamal M, Kareem HS. Clinical effects of “pioglitazone,” an insulin sensitizing drug, on psoriasis vulgaris and its co-morbidities, a double blinded randomized controlled trial. *J Dermatolog Treat* 2015;26:208–214. doi: 10.3109/09546634.2014.932324.
- Lajevardi V, Hallaji Z, Daklan S, Abedini R, Goodarzi A, Abdolreza M. The efficacy of methotrexate plus pioglitazone vs. methotrexate alone in the management of patients with plaque-type psoriasis: a single-blinded randomized controlled trial. *Int J Dermatol* 2015;54:95–101. doi: 10.1111/ijd.12585.

23. Mittal R, Malhotra S, Pandhi P, Kaur I, Dogra S. Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol* 2009;145:387–393. doi: 10.1001/archdermatol.2009.5.
24. Shafiq N, Malhotra S, Pandhi P, Gupta M, Kumar B, Sandhu K. Pilot trial: pioglitazone versus placebo in patients with plaque psoriasis (the P6). *Int J Dermatol* 2005;44:328–333. doi: 10.1111/j.1365-4632.2005.02504.x.
25. Singh S, Bhansali A. Randomized placebo control study of insulin sensitizers (metformin and pioglitazone) in psoriasis patients with metabolic syndrome (topical treatment cohort). *BMC Dermatol* 2016;16:12. doi: 10.1186/s12895-016-0049-y.
26. Chang G, Wang J, Song J, Zhang Z, Zhang L. Efficacy and safety of pioglitazone for treatment of plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials. *J Dermatolog Treat* 2019;1–7. doi: 10.1080/09546634.2019.1610552. [Epub ahead of print].
27. Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. *J Eur Acad Dermatol Venereol* 2012;26 (Suppl 2):12–20. doi: 10.1111/j.1468-3083.2011.04411.x.
28. Salman A, Yucelten AD, Sarac E, Saricam MH, Perdahl-Fis N. Impact of psoriasis in the quality of life of children, adolescents and their families: a cross-sectional study. *An Bras Dermatol* 2018;93:819–823. doi: 10.1590/abd1806-4841.20186981.
29. Wu C, Jin HZ, Shu D, Li F, He CX, Qiao J, *et al.* Efficacy and safety of Tripterygium wilfordii hook F versus acitretin in moderate to severe psoriasis vulgaris: a randomized clinical trial. *Chin Med J* 2015;128:443–449. doi: 10.4103/0366-6999.151069.
30. Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2014;170:274–303. doi: 10.1111/bjd.12663.
31. Mikhaylov D, Hashim PW, Nektalova T, Goldenberg G. Systemic psoriasis therapies and comorbid disease in patients with psoriasis: a review of potential risks and benefits. *J Clin Aesthet Dermatol* 2019;12:46–54.
32. Rønholt K, Iversen L. Old and new biological therapies for psoriasis. *Int J Mol Sci* 2017;18:2297. doi: 10.3390/ijms18112297.
33. Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995;32:982–986. doi: 10.1016/S0190-9622(96)90764-1.
34. Lindegård B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. *Dermatologica* 1986;172:298–304. doi: 10.1159/000249365.
35. Gelfand JM. Psoriasis, type 2 diabetes mellitus, and obesity: weighing the evidence. *JAMA Dermatol* 2016;152:753–754. doi: 10.1001/jamadermatol.2016.0670.
36. Reynoso-von Drateln C, Martínez-Abundis E, Balcázar-Muñoz BR, Bustos-Saldaña R, González-Ortiz M. Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. *J Am Acad Dermatol* 2003;48:882–885. doi: 10.1067/mjd.2003.446.
37. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006;55:829–835. doi: 10.1016/j.jaad.2006.08.040.
38. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006;298:321–328. doi: 10.1007/s00403-006-0703-z.
39. Ip W, Kirchhof MG. Glycemic control in the treatment of psoriasis. *Dermatology* 2017;233:23–29. doi: 10.1159/000472149.
40. Su YJ, Chen TH, Hsu CY, Chiu WT, Lin YS, Chi CC. Safety of metformin in psoriasis patients with diabetes mellitus: a 17-year population-based real-world cohort study. *J Clin Endocrinol Metab* 2019;104:3279–3286. doi: 10.1210/je.2018-02526.
41. Xuan THT, Thi VB, Ngoc AT, Van ED, Dang QT, Van TN, *et al.* Quality of life in psoriasis vietnamese patients treated with metformin in combination with methotrexate. *Open Access Maced J Med Sci* 2019;7:302–303. doi: 10.3889/oamjms.2019.066.
42. Xu X, Lin L, Chen P, Yu Y, Chen S, Chen X, *et al.* Treatment with liraglutide, a glucagon-like peptide-1 analogue, improves effectively the skin lesions of psoriasis patients with type 2 diabetes: a prospective cohort study. *Diabetes Res Clin Pract* 2019;150:167–173. doi: 10.1016/j.diabres.2019.03.002.
43. Mössner R, Schulz U, Krüger U, Middel P, Schinner S, Füzesi L, *et al.* Agonists of peroxisome proliferator-activated receptor gamma inhibit cell growth in malignant melanoma. *J Invest Dermatol* 2002;119:576–582. doi: 10.1046/j.1523-1747.2002.01861.x.
44. Ramot Y, Mastrofrancesco A, Camera E, Desreumaux P, Paus R, Picardo M. The role of PPAR γ -mediated signalling in skin biology and pathology: new targets and opportunities for clinical dermatology. *Exp Dermatol* 2015;24:245–251. doi: 10.1111/exd.12647.
45. El-Gharabawy RM, Ahmed AS, Al-Najjar AH. Mechanism of action and effect of immune-modulating agents in the treatment of psoriasis. *Biomed Pharmacother* 2017;85:141–147. doi: 10.1016/j.biopha.2016.11.105.
46. Bishop-Bailey D. PPARs and angiogenesis. *Biochem Soc Trans* 2011;39:1601–1605. doi: 10.1042/BST20110643.
47. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–2471. doi: 10.1056/NEJMoa072761.
48. Mendes D, Alves C, Batel-Marques F. Number needed to harm in the post-marketing safety evaluation: results for rosiglitazone and pioglitazone. *Pharmacoevidenciol Drug Saf* 2015;24:1259–1270. doi: 10.1002/pds.3874.
49. Lee EJ, Marcy TR. The impact of pioglitazone on bladder cancer and cardiovascular events. *Consult Pharm* 2014;29:555–558. doi: 10.4140/TCP.n.2014.555.
50. Saha S, New LS, Ho HK, Chui WK, Chan EC. Direct toxicity effects of sulfo-conjugated troglitazone on human hepatocytes. *Toxicol Lett* 2010;195:135–141. doi: 10.1016/j.toxlet.2010.03.010.

How to cite this article: Zhang JZ, Ding Y, Xiang F, Yu SR, Zhang DZ, Guan MM, Kang XJ. Effectiveness and safety of different doses of pioglitazone in psoriasis: a meta-analysis of randomized controlled trials. *Chin Med J* 2020;133:444–451. doi: 10.1097/CM9.0000000000000642