

METFORMIN THERAPY FOR ACNE VULGARIS AMONG MALES AND FEMALES WITHOUT POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives: There is an association between Acne vulgaris and insulin resistance and metabolic syndrome. Although metformin was effective in polycystic ovary syndrome (PCOS) patients, its effects on acne vulgaris among males and females without PCOS are scarce. The study aimed to assess the impact of metformin on acne vulgaris among males and females without PCOS.

Methods: We searched seven databases including Scopus, Web of Science, PubMed, Google Scholar, MEDLINE, EBSCO, and Cochrane Library. We conducted the literature search during October and November of 2024 and the articles were included from inception up to the most recently published research. We used the keywords metformin, doxycycline, tetracycline, isotretinoin, acne vulgaris, acne severity, inflammatory lesions, non-inflammatory lesions, and Global Acne Grading System. A checklist was used to collect the information analyzed by the RevMan System 5.4 (United Kingdom).

Results: Out of a hundred and forty-eight studies identified, we screened 27 full texts, and only five studies were found eligible to be included in the meta-analysis. The studies included 214 patients with study duration of 2–6 months. Metformin was effective in reducing global acne severity scores. However, it was inferior to doxycycline, tetracycline, and isotretinoin, odd ratio, 1.16, 95% CI, 0.37–1.94, Chi-square, 3.95, and $p=0.004$, and odd ratio, 3.75, 95% CI, 1.85–5.65, Chi-square, 98.32, and $p<0.001$, respectively.

Conclusion: Metformin was effective in acne vulgaris treatment among males and females without PCOS, $p<0.05$, but not superior to other systemic therapies. $p>0.05$. Furthermore, extensive controlled trials are recommended.

Keywords: Acne vulgaris, Metformin, Doxycycline, Tetracycline, Isotretinoin.

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INTRODUCTION

Metformin was the first-line antidiabetic drug for type 2 diabetes. However, the drug was pushed to the sidetrack and at present, sodium-glucose cotransporter inhibitors and glucagon-like peptide agonists are the first-line among patients with/at high risk of cardiovascular disease, but metformin improves a wide range of diseases including cancer, neurodegenerative diseases, and prolong longevity [1,2]. A metformin acts through inhibition of mammalian targets for rapamycin to improve insulin sensitivity, protects the mitochondria and blood vessels, and suppress pro-inflammatory pathways. Therefore, metformin positively influence various diseases other than type 2 diabetes [3].

Another mechanism of action for metformin is the activation of Adenosine Monophosphate-Activated Protein Kinase, which decreases insulin output from hepatocytes, and advanced glycation products [4]. Because of the above metformin might be effective in acne vulgaris through anti-inflammatory and insulin-sensitizing properties.

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that might be disfiguring by papules, nodules, and scarring [5]. It is ranked number eight among all diseases with a prevalence of 9.4% worldwide [6]. Acne vulgaris is one of the most common diseases that affects all age groups, but adolescents and females are more commonly affected [7]. The pathogenesis is mainly through Propionibacterium colonization, high sebum production, inflammation, and hyperactive

cornification of the pilosebaceous duct [8]. In addition to physical impact, acne has great psychological burden. Patients with acne had a high rate of depression, social isolation, and suicide [9]. Insulin resistance plays a role in the pathogenesis of acne; therefore, metformin as an insulin sensitizer might decrease the severity of acne [10]. Acne and diabetes could share the pathogenesis of insulin resistance, because of that metformin and by increasing insulin sensitivity is attractive in patients with diabetes, metabolic syndrome, and insulin resistance [11]. Several studies concluded the association of acne and metabolic syndrome components including diabetes, hypertension, dyslipidemia, and obesity [12–14]. Melnik *et al.* found a high activity of growth factor-sensitive kinase mTORC1 among patients with acne in comparison to those patients without the disease linking acne to insulin resistance and diabetes [15]. Metformin effects on androgen output, improving insulin sensitivity, anti-inflammatory, and anti-scarring properties could be beneficial in patients with acne, studies assessing the role of metformin in acne were conducted among women with polycystic ovary syndrome (PCOS) [16]. Few studies have addressed the role of metformin among men and women without PCOS. This is the first meta-analysis to investigate metformin in acne vulgaris treatment among patients without PCOS to the best of our knowledge. Therefore, a meta-analysis on the role of metformin among men and women without PCOS is highly justifiable. Therefore, we went ahead to conduct this meta-analysis. Although metformin is effective in treating acne among women with polycystic ovary disease, however, literature

regarding its role in acne among men and women without PCOS is scarce. Metformin was an effective drug for acne vulgaris among males and females without PCOS, but not superior to doxycycline, tetracycline, and isotretinoin. Metformin can be used as a treatment for acne among males and females without PCOS when other drugs are not effective or contraindicated. We aimed to assess the effects of metformin on acne severity in males and females without PCOS and compare it with doxycycline and isotretinoin.

METHODS

This meta-analysis was conducted with extreme adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations Fig. 1.

Study design and duration

This meta-analysis was completed in October and November of 2024.

Inclusion criteria

We included randomized trials and prospective studies assessing the effects of metformin on moderate to severe acne vulgaris among males and females without PCOS.

Exclusion criteria

We didn't include retrospective studies, case-control, and cross-sectional studies. In addition, we excluded case reports and series, experts' opinions, editorials, and reviews from the study. Studies conducted on women with PCOS and androgen excess were not included.

Outcome measures

- The effects of metformin on the severity of acne vulgaris among males and females without PCOS
- The effects of metformin in comparison to doxycycline and isotretinoin on acne severity among males and females without PCOS.

Acne severity assessment

In the present meta-analysis, acne severity was assessed using the global acne grading system (GAGS). The acne grading system provides a relevant clinical evaluation and is highly correlated with treatment choices [17].

Literature strategy

We searched seven databases including Scopus, Web of Science, PubMed, Google Scholar, MEDLINE, EBSCO, and Cochrane Library. We conducted

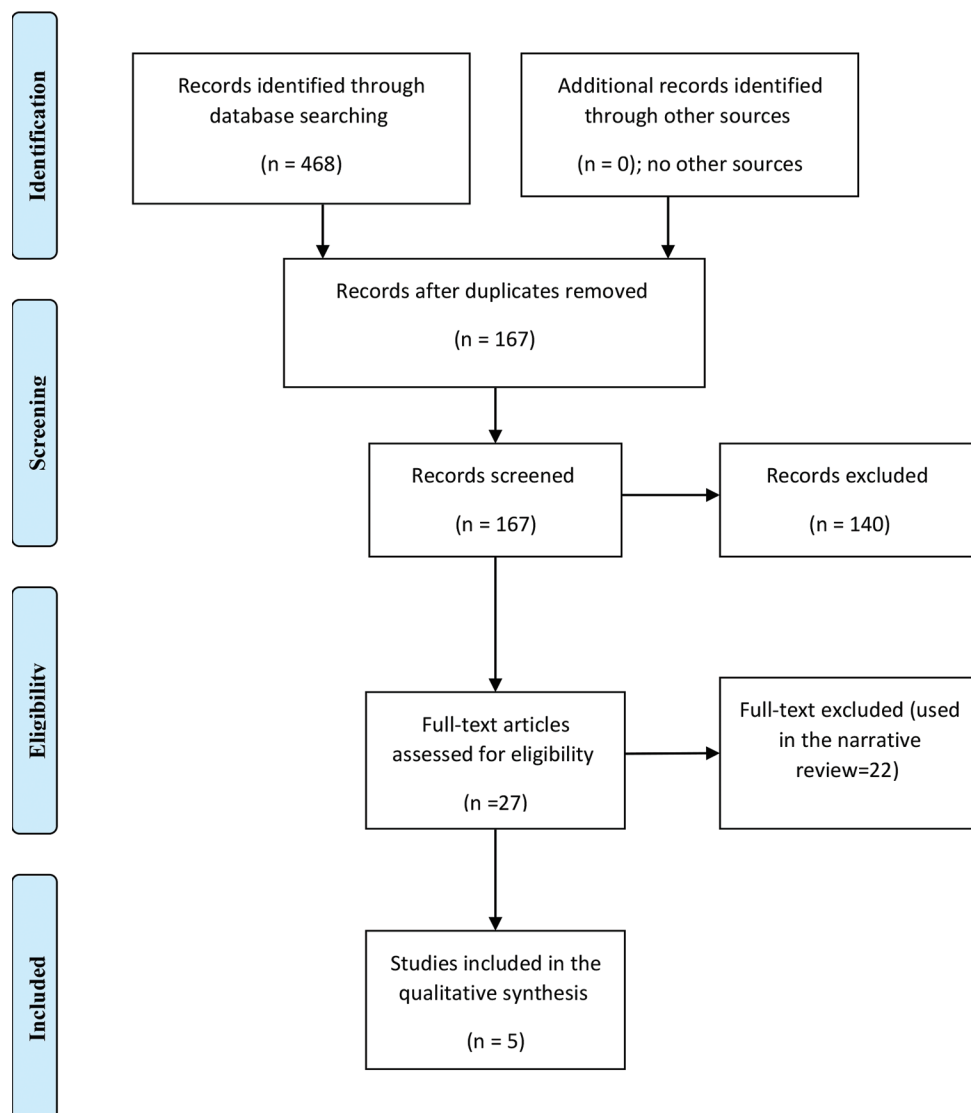


Fig. 1: Studies assessing the role of metformin in acne treatment (The preferred reporting items for systematic reviews and meta-analyses chart)

the literature search during October and November of 2024 and we included the articles from inception up to the recently published research. We used the keywords metformin, doxycycline, tetracycline, isotretinoin, acne vulgaris, acne severity, inflammatory lesions, non-inflammatory lesions, and GAGS. We retrieved four hundred and forty-eight studies, and one hundred and sixty-seven remained after we removed duplication, out of them we screened 27 full texts. However, we found only five articles met the proposed inclusion and exclusion criteria.

Rayyan (QCRI) was used to find duplicates. We applied the inclusion and exclusion criteria to filter the combined search results and also to assess the titles and abstracts' relevance. We conducted a thorough evaluation of manuscripts that met the criteria for inclusion.

We used a structured checklist to collect the required information including the authors' name, study type, publication year, country, study duration, metformin dose and side effects, and adjuvant acne therapy. Furthermore, the Global acne severity score at baseline and following metformin, doxycycline, tetracycline, and isotretinoin were reported.

Strategy for data synthesis

We made summary tables to utilize data from the relevant research, and we chose data from the included study articles once the data from the systematic review was extracted Tables 1-4.

Risk of bias assessment

We used a modified Cochrane Risk of Bias and Newcastle Ottawa scales [18,19]. All the included studies are found to be of good quality (Table 5).

Statistical analysis

For the meta-analysis, we used the RevMan system, version, 5.4 (United Kingdom), and analyzed the continuous data from the five included studies. We entered references and data manually, and then we estimated the Chi-square to assess the level of heterogeneity. For >50% heterogeneity, the random effect will be used otherwise the fixed effect was chosen. We used the fixed effect (because of the non-significant heterogeneity) to the effects of metformin on acne severity. However, the random effect was chosen to compare the effects of metformin, doxycycline, and tetracycline due to the significant heterogeneity. A p-value will be considered significant if <0.05.

RESULTS

Characteristics of the included studies

There were five studies (four trials and one prospective cohort), four studies were published in Asia, and one in Europe [20-24]. The studies included 214 patients and assessed the effect of metformin on acne severity; in addition, the studies compared the effectiveness of

Table 1: Characteristics of the included studies

Author	Study type	Patients	Study duration	Results
Elham <i>et al.</i> 2019 [20]	Randomized trial	Seventy females with resistant acne	6 months on metformin or isotretinoin	Change in acne severity by GAGS
Fabbrocini <i>et al.</i> 2016 [21]	Randomized trial	Twenty males with acne	6 months on metformin and hypocaloric diet versus placebo	Change in acne severity by a global score
Robinson <i>et al.</i> 2019 [22]	Randomized trial	Eighty-four patients with moderate/severe acne	3 months on metformin or tetracycline+benzoyl peroxide	Change in acne severity by a global score
Sadati <i>et al.</i> 2023 [23]	Randomized trial	Forty patients with acne	2 months on metformin or doxycycline	Change in acne severity by GAGS
Kamboj <i>et al.</i> 2023 [24]	Prospective cohort	Thirty patients with acne	3 months on metformin	Change in acne severity by GAGS

GAGS: Global acne grading system

Table 2: The study duration, dose of metformin, control therapy, insulin resistance, reported side effects, and adjuvant therapy among patients with acne vulgaris

Author	Study duration	Gender and glucose profile	Metformin dose	Control group	Side effects	Other therapies
Elham <i>et al.</i> 2019 [20]	6 months	Females with resistant acne, glucose status not reported.	Metformin 500 mg twice daily	Isotretinoin 20 mg, every other day	Not assessed	None
Fabbrocini <i>et al.</i> 2016 [21]	6 months	Males, impaired fasting blood glucose	500 mg twice daily and hypocaloric diet	Symptomatic anti-acne therapy	No reported side effects	Symptomatic anti-acne therapy
Robinson <i>et al.</i> 2019 [22]	3 months	Normal adults (70.2%) females.	Metformin 850 mg daily in combination with topical benzoyl peroxide and oral tetracycline	Oral tetracycline 250 mg twice and topical benzoyl peroxide 2.5%	Gastrointestinal side effects in 31.7% resolved in 2 weeks	Oral tetracycline 250 mg twice and topical benzoyl peroxide 2.5%
Sadati <i>et al.</i> 2023 [23]	2 months	Normal adults (87.5%) females.	Metformin 500 mg tablets twice daily	Doxycycline 100 mg capsules daily,	Minor gastrointestinal side effects	5% benzoyl peroxide
Kamboj <i>et al.</i> 2023 [24]	3 months	Normal individuals	Metformin 1000 mg daily)	None	No reported side effects	No other therapy

Table 3: The effects of metformin on the global acne grading system

Author	Country	Metformin (Mean±SD)	Control (Mean±SD)	Results
Fabbrocini <i>et al.</i> 2016 [21]	Italy	7±1.5	5.5±0.2	Significant
Robinson <i>et al.</i> 2019 [22]	Malaysia	4.82±3.39	4.22±3.56	Not significant
Sadati <i>et al.</i> 2023 [23]	Iran	10.65±6.29	14.95±12.89	Not significant

metformin with doxycycline, tetracycline, and isotretinoin. The duration of the studies ranged from 2 to 6 months. All the patients were not diagnosed with PCOS. The dose of metformin was 850–1000 mg/day, four studies used metformin alone and one study used metformin with tetracycline. The included patients were males with impaired fasting glucose, the other study populations were males and females without PCOS or impaired glucose profile. Regarding metformin side effects, two studies reported minor gastrointestinal side effects, two reported no adverse effects, and the side effects were not mentioned in one study. The adjuvant therapy was 5% benzoyl peroxide in two studies, symptomatic acne treatment in one study, and no adjuvant therapy in the remaining two studies.

There are three studies in the present meta-analysis that assessed the effect of metformin on the GAGS and was found to be effective, odd ratio, 1.16, 95% CI, 0.37–1.94, Chi-square, 3.95, and $p=0.004$. The three studies showed a non-significant heterogeneity (I^2 for heterogeneity=49%, p -value for heterogeneity, 0.14, the standard difference=2), Fig. 2.

Although metformin was an effective acne treatment, however, it was inferior to doxycycline, tetracycline, and isotretinoin, odd ratio, 3.75, 95% CI, 1.85–5.65, Chi-square, 98.32, and $p<0.001$. The four studies included in the present meta-analysis showed substantial heterogeneity (I^2 for heterogeneity=97%, the p -value for heterogeneity <0.001 , the standard difference=3, Fig. 3).

DISCUSSION

In the present meta-analysis, metformin was effective in reducing acne global scores among males and females without PCOS. However,

metformin was less effective than doxycycline, tetracycline, and isotretinoin (odd ratio, 1.16, 95% CI, 0.37–1.94, and odd ratio, 3.75, 95% CI, 1.85–5.65, respectively). The above results imply that metformin can be used as adjuvant therapy (among males and females without PCOS). In addition, the drug can be used when other treatments are not effective or contraindicated. A previous meta-analysis observed the efficacy of metformin (as adjuvant therapy) for acne among females with PCOS [25]. This meta-analysis is possibly the first study to assess the role of metformin and included both women and men without PCOS. The present findings supported the results of a previous systematic review including three studies [26]. However, the author included a conference paper that limited their results [27]. In addition, important trials were published since that time. Further reviews targeted metformin use in dermatological diseases among patients with PCOS, Sung et al. included only one trial among those without PCOS and recommended further studies with good sample size and controlling for confounders including diet [28]. Monte-Serrano et al. [29] conducted a systematic review in Spain. However, they discussed the findings of other reviews and one trial [17]. Nguyen et al. [30] reviewed the literature recently and included the metformin benefits in patients with acne, but we included the benefits in patients with PCOS.

The rationale of metformin use in acne vulgaris

The physiologic insulin resistance during puberty induces hyperinsulinemia, high androgens, and high insulin-like growth factor-1 (IGF-1). IGF-1 stimulates sebocyte proliferation and sebum excretion [29]. In addition, hyperinsulinemia mediates acne formation through epidermal growth factor and transforming growth factor β . Furthermore, non-esterified free fatty acids promote inflammation and colonization by cutibacterium acne [30]. Therefore, insulin resistance plays an important role in the pathogenesis of acne vulgaris.

Table 4: A comparison between metformin and other acne treatment on the global acne grading system

Author	Country	Metformin (Mean \pm SD)	Control (Mean \pm SD)	Results
Elham et al. 2019 [20]	Iran	26.2 \pm 8.4	11.3 \pm 9.2	Significant
Fabbrocini et al. 2016 [21]	Italy	25.1 \pm 8.9	14.1 \pm 10.4	Significant
Sadati et al. 2023 [23]	Iran	13.45 \pm 4.22	24.10 \pm 6.93	Significant
Kamboj et al. 2023 [24]	India	19.8 \pm 5.36	13 \pm 5.79	Significant

Table 5: Assessment of the risk of bias for the included randomized controlled trials depending on Cochrane risk of bias

Author	Selection bias ¹	Selection bias ²	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Elham et al. 2019 [20]	Low	Low	Low	Low	Low	Low	low
Fabbrocini et al. 2016 [21]	Low	Low	Some concerns	Low	Some concerns	Low	Low
Robinson et al. 2019 [22]	Low	Low	Some concerns	Low	Some concerns	Low	Low
Sadati et al. 2023 [23]	Low	Low	Low	Low	Some concerns	Low	Low

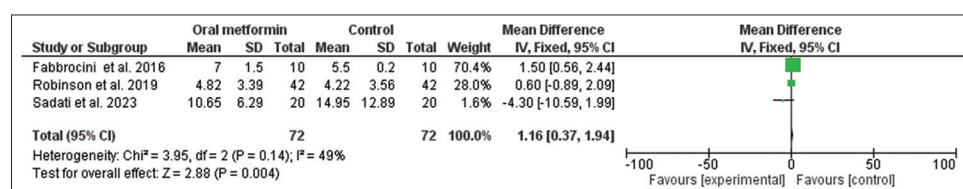


Fig. 2: Metformin effect on acne vulgaris

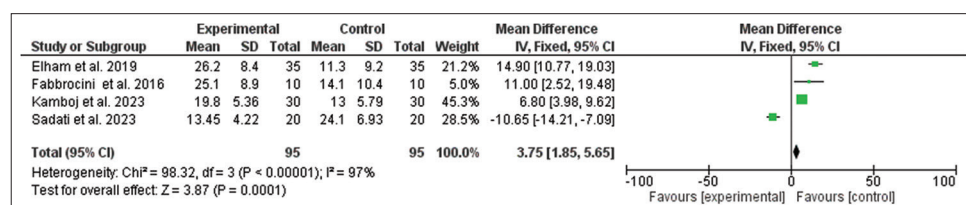


Fig. 3: Metformin versus other therapies' effect on acne vulgaris

Metformin and insulin sensitization might block the cross-talk between insulin resistance and acne vulgaris. Importantly, acne vulgaris is associated with the components of metabolic syndrome including insulin resistance, high blood pressure, dyslipidemias, and cardiovascular disease [31]. Thus, metformin is an effective treatment for acne with no reported severe side effects [10, 12]. Although metformin is inferior to other systemic therapies for acne, it can be used as an adjuvant or when the other drugs are contraindicated or not effective. Doxycycline, tetracycline, and isotretinoin are contraindicated in pregnancy, lactation, and children < 8 years [32,33]. Oral contraceptives are not the right choice for women desiring pregnancy.

The study limitations

This meta-analysis's strength is that it was the first meta-analysis to investigate the effectiveness of metformin in acne vulgaris treatment. However, there are several limitations that face the present results, the small number of included studies and the significant heterogeneity of the results. A major limitation of this meta-analysis is that most of the included studies did not control for insulin resistance.

CONCLUSION

Metformin was effective for moderate/severe acne vulgaris among males and females without PCOS. However, the drug was inferior to doxycycline, tetracycline, and isotretinoin. The dose of metformin ranged from 850 to 1000 mg/day and gastrointestinal side effects were reported among some metformin users. The adverse effects were well-tolerated and the patients preferred to continue metformin. Therefore, metformin can be used as adjuvant therapy among males and females without PCOS or when other drugs are contraindicated or not effective. Metformin can be repurposed for the treatment of acne vulgaris in particular for patients with diabetes and metabolic syndrome offering both the patients and physician a new option for acne treatment. Further larger studies investigating the effectiveness of metformin in acne vulgaris treatment among patients without insulin resistance are suggested.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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CONTRIBUTION OF AUTHORS

Dr. Ahmed Hamad Sulaiman and Dr. Hyder Mirghani, involved in the collection of articles, statistical analysis, manuscript writing, and final editing of the manuscript. Dr. Omaira A Hamid, Dr. Hafiz Osman Ibnidris Almisbah, and Dr. Haider Osman Ibn Idris Elmisbah involved in the collection of articles, manuscript writing, and statistical analysis. Dr. Abdelrahman Mohamed Ahmed Abukanna involved in the final screening of articles editing and proofreading. All authors revise and approve the final version of the manuscript.

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