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Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris

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Abstract

The purpose of this literature review is to evaluate the use of metformin as an adjunct therapy in the treatment of moderate-to-severe acne in those not diagnosed with polycystic ovary syndrome (PCOS) or androgen excess. The authors conducted independent literature searches. Results were limited to clinical trials and randomized controlled trials. Studies with participants diagnosed with moderate-to-severe acne vulgaris taking metformin versus placebo or other active treatment were included; studies with participants diagnosed with PCOS or androgen excess were excluded. The authors found three studies consistent with the search guidelines that evaluated the effects of metformin as adjunct therapy in moderate to severe acne vulgaris. In each study, metformin was an effective adjunct therapy in the treatment of moderate-to-severe acne vulgaris.

Keywords: metformin, acne vulgaris, low glycemic diet, insulin resistance, IGF-1

Introduction

Acne vulgaris is a common, but complex skin disorder with multiple factors affecting about 50 million people in the United States [1]. It mainly involves the chronic inflammation and hyperkeratosis of the pilosebaceous follicles, increased sebum secretion, and colonization of *Propionibacterium acnes* [2]. Increased sebum secretion begins during puberty in tandem with peaking growth hormone levels and insulin-like growth factor (IGF-1), [3, 4]. Dietary factors may also play a role as it has been found to

exist in countries that have diets consisting of high glycemic loads, saturated fats, and high amounts of dairy proteins [5, 6, 7].

The association between acne vulgaris and insulin resistance is well known in females with polycystic ovary syndrome (PCOS), [8]. PCOS is among the most prevalent endocrinological disorders in females of reproductive age. It has multisystemic symptoms such as acne, irregular menses, hyperandrogenism, seborrhea, hirsutism, insulin resistance, and female-type androgenetic alopecia [4, 9]. Acne is seen in approximately 15-30% of adult women with PCOS [10]. Lifestyle modification, insulin sensitizers, oral contraceptives, and vitamin D supplementation are the most common therapeutic tools for the management of PCOS [11].

Recently, studies support the role of insulin resistance in male patients and female patients independent of hyperandrogenemia with acne vulgaris and post-adolescent acne [4, 5, 8, 12, 13].

Metformin is an oral antihyperglycemic agent often used to treat overweight type 2 diabetic patients. It decreases hepatic glucose output and increases glucose utilization by muscles and adipocytes by increasing insulin sensitivity [9]. It is a derivative of the French lilac plant and was used in herbal medicine prior to the 20th century. There are few adverse side effects with metformin, including diarrhea, indigestion, and nausea; it is relatively safe in pregnancy [14]. Metformin has been found to improve acne severity in those suffering from PCOS [9, 14].

Standard therapies for acne include topical retinoids (tretinoin, adapalene, tazarotene), benzoyl peroxide (alone or in combination with topical antibiotics), and oral contraceptives for girls and women. For moderate and severe acne that does not respond to topical therapies, the use of oral antibiotics such as tetracyclines and macrolides is recommended. Owing to the increased risk of bacterial resistance, antibiotics as the sole therapy is not recommended for long durations [1].

In this article, we examine the use of metformin as an adjunct therapy to moderate and severe acne in those not diagnosed with PCOS or androgen excess.

Methods

We searched MEDLINE, Google Scholar, Grey Literature Report, Cochrane Central Register for Controlled Trials, University of York Centre for Reviews and Dissemination CRD database, and Clinicaltrials.gov with no date restrictions. We also searched abstract books and poster abstracts of several dermatological conferences held from January 1, 2015 to November 30, 2016, including the 23rd World Congress of Dermatology and American Academy of Dermatology Electronic Posters. Owing to the sparse results in the database searches, we limited the abstract book and poster abstract search. We hand-searched the 22nd Regional Conference of Dermatology (Asian-Australasian) Abstract Book and the 2016 World Congress Fund Poster Abstract Book. We limited our search to randomized controlled trials with participants with an established diagnosis of moderate-to-severe acne vulgaris taking metformin versus placebo or other active treatment. We excluded any studies with participants diagnosed with PCOS or androgen excess. There was no limitation based on the language of the publication. The two study authors performed the searches independently and found identical results.

For the Medline search, the search term "metformin AND acne" was used with a filter for article types set to Clinical Trial and Randomized Clinical Trial. For the Google Scholar search, the search parameter used was "allintitle: metformin acne." For the Grey Literature Report search, the search term used was "metformin acne." For the Cochrane Central Register for Controlled Trials search, the search term

"metformin AND acne" was used with a filter for result type of "Title, Abstract, Keywords." For the University of York Centre for Reviews and Dissemination CRD database, the search parameters used were "Any field = metformin AND Any field = acne." For the Clinicaltrials.gov database, the search term used was "metformin AND acne."

For the 23rd World Congress of Dermatology search, the search term used was "metformin." For the 22nd Regional Conference of Dermatology (Asian-Australasian), we hand-searched the abstract book for "metformin." For the American Academy of Dermatology Electronic Posters database, we searched all meetings since January 2015 using "Category: Acne." We then hand-searched the results for the keyword "metformin."

Results

Three studies were identified after duplicates were removed and deemed relevant. Each study measured the change in acne vulgaris, comparing metformin as an adjunct to a standard therapy in a prospective, controlled, randomized study design. All results were written in English. The 3 trials reported data on a total of 144 patients and 6 sets of interventions. Bibliographies of the search results were screened for further relevant papers.

Fabbrocini et al. [15], evaluated metformin as an adjunct treatment to a hypoglycemic diet in patients with altered metabolic profile. Altered metabolic profile was defined as raised levels of total and low-density lipoprotein cholesterol, reduced levels of high-density lipoprotein (HDL) cholesterol, impaired fasting glucose, and body mass index (BMI) and waist circumference at the upper limit of normal. Inclusion criteria were males aged between 17-24 years, with acne for at least 1 year which was resistant to common therapies. Common therapies were defined as oral antibiotics and retinoids, and topical antibacterials and retinoids. Exclusion criteria were a presence of endocrinological diseases or other dermatological diseases. They randomly divided 20 patients with altered metabolic profile and met inclusion criteria into two groups of 10 patients. One group received 500mg metformin twice daily, a hypocaloric diet (1500 – 2000 kcal), and symptomatic anti-acne treatment for 6 months. The symptomatic anti-acne treatment

consisted of bland detergent and a sebostatic cream based on azelaic acid and nicotinamide. The second group only received the symptomatic anti-acne treatment for 6 months. Global Acne Grading System (GAGS) was used to measure acne severity. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was used to estimate insulin resistance. Waist and hip circumferences, waist to hip ratio (WHR), BMI, HDL and total cholesterol, fasting blood glucose and insulin, and oral glucose tolerance test (OGTT) were measured at baseline and after 6 months of treatment. GAGS was statistically significantly decreased in the metformin group ($p < 0.03$) versus the symptomatic treatment-only group in which GAGS was not significantly decreased ($p = 0.06$). OGTT was significantly decreased in the metformin group ($p = 0.04$). In both groups, BMI and WHR was positively correlated with GAGS at baseline; higher BMI and WHR correlated with higher GAGS values. In the metformin group, there was a statistically significant positive correlation for HOMA-IR and GAGS from baseline to after 6 months of treatment ($p < 0.03$). No adverse events related to the metformin were reported [15].

Gabaton et al. [16, 17], evaluated metformin as an adjunct treatment to lymecycline and adapalene + benzoyl peroxide gel. They randomly divided 40 patients with moderate to severe acne vulgaris into two groups both receiving lymecycline for 6 weeks and adapalene + benzoyl peroxide gel for 18 weeks. One group received metformin as the adjunct treatment for 18 weeks. The second group received a placebo as the adjunct treatment for 18 weeks. Mean reduction rates of non-inflammatory, inflammatory, and total lesion counts, Dermatology life quality index (DLQI) score, subjective self-assessment score, modified global severity score, and cutaneous and systemic adverse events were determined biweekly. Both groups had comparable mean reduction rates of the non-inflammatory lesion count ($p > 0.05$). Mean reduction rates of the inflammatory and total lesion count were higher in the metformin group versus the placebo group ($p < 0.05$). Both groups had decreased mean DLQI scores ($p < 0.0001$). Both groups had comparable results with improved subjective self-assessment scores. The mean modified global severity score was lower in the metformin group versus the placebo group ($p = 0.034$). Cutaneous adverse events

were tolerable and included erythema, pain, dryness, and scaling. Systemic adverse events were self-limited and included flatulence, headache, diarrhea, and epigastric pain [16, 17].

Robinson and Affandi [18] evaluated metformin as an adjunct treatment to topical benzoyl peroxide and oral tetracycline. They randomly divided 84 patients with moderate to severe acne vulgaris into two groups of 42. One group received 850 mg of metformin daily along with topical benzoyl peroxide 2.5% and oral tetracycline 250 twice daily. The second group received only the topical benzoyl peroxide 2.5% and oral tetracycline 250 twice daily. Acne lesion counts, treatment success rate, and Cardiff Acne Disability Index (CADI) scores were determined. Treatment success rate was determined as the percentage of patients with an Investigator Global Assessment score of 0 or 1 or improvement of two grades from baseline. This was significantly higher in the metformin group at 66.7% versus the control group at 43.2% ($p = 0.04$). At week 12, the mean percentage reduction in total lesion counts from baseline was greater in the metformin group at -71.4% versus the -65.3% in the control group ($p = 0.278$). At week 12, the CADI scores indicated a mean reduction was greater in the metformin group at -4.8 versus -4.2 in the control group ($p = 0.451$). There were gastrointestinal symptoms reported in 31.7% of the metformin group [18].

Discussion

This evidence-based literature review highlights the limited amount of high quality, randomized, placebo-controlled trials investigating the effects of metformin as an adjunct therapy for acne treatment using clinically objective measures in those not diagnosed with PCOS. Included studies were of limited sample size. They were not conducive to pooled analysis owing to the different standard therapies of each study. Future studies should include more participants with longer follow up periods to support its use.

Conclusion

Metformin may be an effective and safe adjunct treatment in the treatment of moderate to severe acne vulgaris.

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