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 ORIGINAL ARTICLE

Oral Metformin for Treating Dermatological Diseases: A Systematic Review

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ABSTRACT

Introduction: Metformin is an antihyperglycemic medication most commonly used to treat type II Diabetes Mellitus with promising off-label application for the treatment of hidradenitis suppurativa, psoriasis, acne, acanthosis nigricans, and hirsutism.

Objective: To comprehensively assess evidence regarding the use of metformin for treating primary cutaneous disorders.

Materials and Methods: A systematic literature search was conducted through PubMed, Cochrane, Web of Science, and CINAHL to identify the role of metformin in primary skin disease.

Results: Sixty-four studies met inclusion criteria. Metformin demonstrates promising clinical response and favorable safety profile for treatment of HS, with most patients experiencing a decrease in frequency or severity of HS flares, and some experiencing full resolution of HS lesions. Patients with psoriasis treated with metformin experienced quantifiable clinical responses. Application of metformin on polycystic ovarian disease (PCOS) related acne, acanthosis nigricans, and hirsutism yielded mixed clinical results. No serious adverse effects were reported.

Conclusion: Metformin is safe and efficacious and may be considered as an adjunctive therapy for the treatment of psoriasis and hidradenitis suppurativa in addition to first line therapies as well as PCOS related acne, acanthosis nigricans, and hirsutism.

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INTRODUCTION

Although metformin is typically employed as a first-line agent for treatment of type II diabetes mellitus (T2DM), it is being increasingly utilized as a therapy for a variety of other conditions including metabolic syndrome, polycystic ovary syndrome (PCOS), hyperandrogenism, and even cancer prevention. Metformin lowers insulin resistance by suppressing hepatic gluconeogenesis while stimulating skeletal myocyte glucose uptake and inhibiting the proinflammatory response and targeting hyperandrogenism. Given its reassuring safety profile, metformin has been increasingly considered for treating diseases associated with inflammatory and metabolic syndrome such as psoriasis, hidradenitis suppurativa (HS), acne, hirsutism, and acanthosis nigricans.

The mechanism of action of metformin is complex and incompletely understood. Metformin is theorized to act primarily via inhibition of mitochondrial function, generating an ATP-deficient environment leading to activation of AMP-activated protein kinase (AMPK) and upregulation of catabolic metabolism. Metformin also dampens the pro-inflammatory response by inhibiting nuclear factor kappa-B (NFκB) via both liver-associated AMPK-dependent and independent pathways, and down-regulates production of nitric oxide (NO), prostaglandin E2 (PGE2), and acute inflammatory markers TNF-α, IL-1, and IL-6. Finally, metformin has been shown to decrease hyperandrogenism, and thought to directly affect hormonal steroidogenesis by modulating ovarian and adrenal androgen output.

While further research to elucidate metformin's myriad downstream effects is needed, metformin remains a promising clinical therapy for dermatologic disease. This systematic review will explore the clinical efficacy of metformin treating various dermatologic conditions, including HS, psoriasis, acanthosis nigricans, acne, and hirsutism.

MATERIALS AND METHODS

Literature Search

This study was done in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[1] A primary literature search was conducted with the databases PubMed, Cochrane, Web of Science, and CINAHL. Two authors independently screened the above-mentioned databases. The search terms used are as follows: PubMed and Cochrane: (metformin OR glucophage OR dimethylguanylguanidine OR dimethylbiguanidine) AND (skin and connective tissue diseases

OR integumentary system OR dermatology OR hair OR nail OR skin); CINAHL: ((MM "Skin and ConnectiveTissue Diseases+") OR (MM "Skin+") OR "skin" OR "hair" OR "nail" OR "dermatology") AND ((MM "Metformin") OR "metformin" OR "glucophage" OR "dimethylguanylguanidine" OR "dimethylbiguanidine"); Web of Science: (metformin OR glucophage OR dimethylguanylguanidine OR dimethylbiguanidine) AND (dermatology OR hair OR nail OR skin). Medical Subject Headings (MeSH®) controlled vocabulary and text words were both utilized to develop the search terms. Systematic literature search was conducted on November 26, 2018 and all articles from the beginning of the databases through that date were eligible for inclusion.

Study Selection and Appraisal

Two reviewers independently screened all article titles and abstracts to include clinical trials, cohort studies, case-control studies, case series, cross-sectional studies, or case reports, written in English, of metformin in human subjects with skin diseases. Animal studies and articles not written in English were excluded. Subsequently identified studies were then subjected to full-text review. Authors were contacted for missing data. Bias risk and methodological quality were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. Rationales for exclusion and article appraisals were recorded at every stage. Final decision on study selection was reached by discussion. References of included and excluded studies were reviewed for potential studies not identified through initial search strategy.

Data Extraction and Analysis

Included studies were summarized using a data extraction form. Studies were graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence.

RESULTS

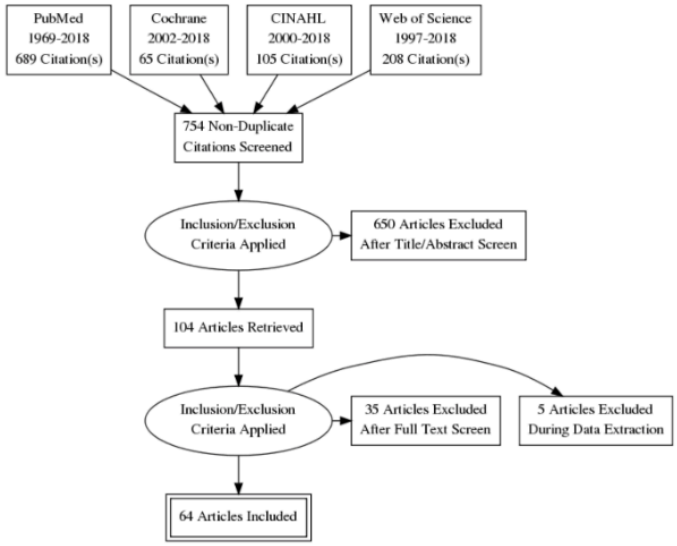
Initially, 754 non-duplicate articles from the years 1969 to 2018 were identified through the above-mentioned search terms across the four literatures databases. After title/abstract screening, 104 articles met criteria for inclusion. These articles were subjected to full-text screen and 64 studies were included in this systematic review as depicted by the PRISMA flow diagram (Figure 1).

Hidradenitis Suppurativa

Oral metformin as treatment for HS has been described only in one prospective cohort study and two case reports (total n=27, age: 17–50 years) with promising clinical response and favorable safety profile.

In one prospective cohort study, 25 patients with HS who were metformin-naive were treated with metformin over 24 weeks, and clinical severity of HS was assessed with both Sartorius and

FIGURE 1. PRISMA flowchart depicting the inclusion and exclusion of articles in this systematic review.



Dermatology Life Quality Index (DLQI) scores obtained at 0, 12, and 24 weeks.[2] Seventy-six percent of patients (n=19) showed steady improvement of their HS lesions, and 24% (n=6) showed no response. The average number of work days lost was reduced from 1.5 to 0.4 and the number of patients that were classified as severely depressed decreased from eleven to four over the treatment period.

Khandalavala's case report described a 19-year-old female with history of PCOS since puberty and an eight-year history of cicatricial HS previously treated unsuccessfully with numerous surgical and medical interventions. After three years of multifactorial treatment with lifestyle modification, oral contraception, dapsone 100mg/day, finasteride 5mg/day, subcutaneous liraglutide, and adding metformin 2000mg/day, the patient was free of new lesions for six months. Study reported complete healing of the axillary lesions, >90% improvement of lesions in her groin, thigh, and perianal region, and 60% improvement of lesions in her thorax and abdomen. Additionally, the patient tolerated treatment without adverse effects.[3]

In another case report, a 50-year-old female with history of seronegative arthritis, T2DM, and 18-year history of HS was stable while on metformin for her T2DM. However, she experienced an HS flare when metformin was discontinued after successful glycemic control through diet. The patient subsequently initiated metformin 500mg/day and noted less frequent and shorter HS flares after three months. At this point, her metformin dose was increased to 1000mg/day, which led to the resolution of her axillary sinuses and leaking abscess along with decreased pain.[4]

Psoriasis

The role of metformin in the treatment and prevention of psoriasis has been studied in three RCTs and one retrospective cohort study (n=73,550). Patients were treated with 1,000 to 1,700mg/day oral metformin. All studies demonstrated positive results in both genders and throughout all age groups.

Singh et al conducted two randomized, open-label, placebo-controlled, single-center trials involving treatment of psoriasis with metformin. The initial study evaluated the efficacy and safety of insulin sensitizers (metformin and pioglitazone) in psoriasis patients with metabolic syndrome, outcomes for which were evaluated by psoriasis area and severity index (PASI, 0-72) and erythema, scaling, and induration (ESI, 0-9) scores. The primary endpoints were changes in PASI, ESI, and physician global assessment (PGA) scores from baseline after 12 weeks of therapy as compared to placebo. Secondary endpoints included the proportion of patients achieving 75% decrease in PASI and ESI scores in each group. The metformin group had significant improvement in PASI (P=0.001), ESI (P=0.016), and PGA (P=0.012) scores. It should be noted that both metformin and pioglitazone treatment groups had a statistically significant proportion of patients achieving 75% decrease in PASI (P=0.001, P=0.001) and ESI (P=0.001, P=0.001) without any adverse events.[5]

Singh et al's more recent study (n=35) investigated the efficacy and safety of metformin in psoriasis patients with metabolic syndrome. Significant improvement in mean percent change of ESI score was observed in the metformin group (P=0.048), whereas no significant percent change was observed in PASI (P=0.215) or PGA scores (P=0.070). There was no statistically significant difference in adverse events between groups with the exception of >1kg weight gain in the placebo group (P=0.042).[6]

A randomized single-blind clinical trial (n=58) investigated efficacy and safety of metformin as an adjunct to methotrexate for treatment psoriatic arthritis (PsA). A significantly higher percentage (41%; n=12 of 29) of the metformin group achieved an 20% improvement in tender and swollen joints (ACR20) at 24 weeks compared to the placebo group (21%; n=6 of 29; (P<0.001), with greater improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) (P<0.005), higher PASI75 (P<0.001), and improvements in psoriatic arthritis response criteria (PsARC) score (P<0.001) at week 24 compared to placebo. There was no significant difference in adverse events between groups.[7]

A case-control study (n=73,404) using the United Kingdom General Practice Research Database (GPRD) to identify patients with a first-time diagnosis of psoriasis and identical number of control subjects, demonstrated that patients who received ≥15 prescriptions of metformin had reduced psoriasis risk (OR 0.77, 95% CI 0.62–0.96).[8]

Acanthosis Nigricans (AN)

The utility of metformin to treat AN in both male and female patients (n=57), age range, 12–45 years old, has been reported in five case reports, one RCT, two prospective cohorts, one retrospective cohort, and one case series. Various doses have been studied in adult patients ranging from 500 to 2000mg daily, as well as weight-based dosing at 25mg/kg/day.[9] Metformin was noted to be an efficacious treatment for AN in 72.2% of patients. Oral metformin was also effective in AN in conjunction with isotretinoin titrated to 40–80mg/day for 2 years, 1.01 units/kg recombinant human insulin-life growth factor (rhIGF1) injections for 5 years, or a carbohydrate-controlled diet for 3 months.[9-11] When compared to other diabetes medications, such as rosiglitazone, patients on metformin had greater improvement in skin texture with minimal clinical response.[12]

Acne

The utility of metformin as a treatment for acne has been described in 11 RCTs and 9 cohort studies. Women with a history of PCOS with acne, and one study involving men with refractory acne, (total n=1,587 patients) were treated with oral metformin (dose range, 1,000–2,550mg/day). All except three studies[13-15] reported significant improvement in acne in female patients with PCOS. Only Fabbrocini et al's study assessed the effects of metformin and a low glycemic diet on male subjects with resistant acne.[16] While the study led to statistically significant improvement in acne in the experimental group receiving metformin and undergoing low glycemic diet (P<0.05), the low sample size (n=20) and lack of stratification necessitates follow-up studies. Metformin was generally well tolerated with the exception of gastrointestinal intolerance (nausea, vomiting, diarrhea, loss of appetite), with only few patients discontinued the studies.[17,18] Although dosage correlation studies were not performed, both obese and lean patients (31.8 vs 11.6%; all P<0.017) with insulin resistance benefited from their metformin treatments over a 6-month period with dose adjustment ranging from 500–1000mg.[19,20]

No improvement was noted in three studies.[18,21,22,23,24] Adding metformin did not lead to significant improvement in acne patients with clinical manifestations of hyperandrogenism and elevated DHEAS experienced a significant decrease in acne score by 14% (P<0.0005).[21] Adding metformin to estrogen and anti-androgen medications (ie, cyproterone acetate or EE-CA) failed to significantly improve acne (P=0.79), suggesting a lack of pharmacological synergy.[18,22,23,24] Both Navali et al's and Fruzzetti et al's studies demonstrated that statins (20mg/day simvastatin and 4 g/day myo-inositol, respectively) are superior to 1.5g/day metformin for treating acne (P<0.05) among other PCOS parameters.[15,25] Combination therapy of metformin 850mg with pioglitazone 7.5mg daily, flutamide 62.5mg daily for 6 months, or oral metformin 850mg twice a day and simvastatin 20mg daily also demonstrated clinical efficacy for improvement in acne

(P<0.05).[26] Interestingly, metformin monotherapy was more efficacious for reducing acne lesion count than combination with calcium and vitamin D.[27]

Hirsutism

One of the most studied conditions involve women with acne and a history of PCOS or HAIR-AN syndrome, (dose range, 1,000–2,550mg daily) in 30 RCTs. Yet it is still difficult to conclude given that reported results vary between studies,[21,22,28-37] whereas no significant improvements were reported in four RCTs, and five prospective cohort studies in the literature.[13,14,19,20,38-42]

Combination therapies of metformin with other agents, including spironolactone, ethinyl estradiol-cyproterone acetate (EE-CA), N-acetylcysteine (NAC), myo-inositol, and other diabetic medications generally led to greater decrease in PCOS than monotherapy alone. Metformin along with hormonal therapies including clomiphene citrate (50mg daily for six cycles), flutamide (250mg twice daily) and combination OCPs, drospirenone with ethinyl estradiol (DRP-EE), led to statistically significant reduction in hirsutism scores. Two other RCTs (n=206) demonstrated greater improvement in hirsutism scores for patients treated with combination therapy: spironolactone 50–100mg daily and metformin.[43,44] Mixed results were obtained when comparing the clinical efficacy measured by hirsutism reduction when treated with metformin monotherapy (dose range, 500mg two to three times daily) versus EE-CA (2 mg daily) across the duration of t3 months to 1 year.[23,24,42,45,46] Of the various combination therapies reported, combination therapy with pioglitazone (7.5mg daily), flutamide (62.5mg daily) and metformin (850mg daily for 6 months) were reported to be the most effective.[18,47-49]

When comparing the role of metformin in the management of hirsutism to other diabetes medications, metformin was superior to pioglitazone (30mg daily for 6 months), but inferior to rosiglitazone (4mg daily for 24 weeks).[50,51] No statistically significant difference in hirsutism reduction was achieved when comparing metformin monotherapy and N-acetyl cysteine (NAC 600mg three times daily for 24 weeks), myo-inositol (4,000mg daily for 6 months), and simvastatin (20mg daily for 3 months).[15,25,52]

In three different studies, three different combination therapies of metformin with five sessions of intense pulsed light therapy (IPL) for 6 months, simvastatin 20mg daily for 6 months and calcium 1,000 mg daily and Vitamin D 50,000 IU for 4 months supplementations improved hirsutism and qualitative patient satisfaction.[26,27,41,53-55]

DISCUSSION

Metformin is a promising therapy for the treatment of cutaneous diseases. This systematic review of 64 studies of its use in cutaneous conditions as both a mono- as well as adjunct therapy suggests that high-dose long-term metformin therapy is beneficial for HS, psoriasis, and acne, while its efficacy for treatment of hirsutism and acanthosis nigricans is less clear. In these studies, oral metformin dosing for treatment of dermatologic diseases was variable, with dosage ranging from 500 to 2,000mg/day over 24 weeks to 3 years. In treatment of diabetes, 500mg represents the suggested starting dose whereas 2,500mg represents the upper limit suggested for patients with severe insulin resistance. As opposed to the studies regarding HS and psoriasis, it should be noted that the studies regarding AN, acne, and hirsutism reviewed primarily involved female patients with PCOS.

Metformin for Hidradenitis Suppurativa (HS)

Albeit the limited sample size and positive publication bias, the clinical outcome for the treatment of HS with metformin are promising in all of the studies reviewed. HS is thought to result from follicular occlusion in combination with underlying immune dysregulation and an overactive toll-like receptor (TLR) response to bacterial colonization.[56] Patients with HS have been found to have elevated CRP, elevated lymphocyte and neutrophil counts, and upregulated cytokine profiles.[57] Interestingly, the acute inflammatory markers TNF-α, IL-1, and IL-6, along with IL-12/23 and TLR ligands found in HS patients are also common amongst psoriasis patients, as both conditions involve the TNF-α induced NF-κB pathway that leads to metabolic dearrangements.[57]

HS is a highly morbid and notoriously difficult condition to manage, and limited treatment options exist. Adalimumab, a TNF-α inhibitor and a first-line therapy for psoriasis, is currently the only FDA-indicated biologic agent approved for the treatment of moderate-to-severe HS in ages 12 and beyond. Other TNF-α inhibitors such as infliximab have also demonstrated efficacy in treatment of HS.[58,59] However, further studies are necessary to better understand not only the efficacy but also pharmacology underlying combining adjunctive therapies on a drug to drug basis.

Metformin for Psoriasis

Long-term use of metformin appears to be useful in prevention as well as management of psoriasis in patients with underlying metabolic syndrome with insignificant side effect. The effect of metformin in patients with lower BMI is less clear, warranting larger sample sizes and better clarification of other potential confounding factors. In practice, clinicians should be mindful of selecting psoriasis patients with metabolic syndrome for adjunctive treatment with metformin for most optimal results.

Scrutinization of the studies reported raises the question whether metformin is the only efficacious adjunctive anti-diabetic agent available. While the study by Rena et al reported that

metformin was the only therapy associated with the reduction of psoriasis risk among other anti-diabetic medications tested (ie, thiazolidinediones, sulfonylureas, biguanides, or acarbose),[8] Ghiasi et al reported that pioglitazone vastly enhances the efficacy of phototherapy in psoriasis patients.[60] Immunologically, thiazolidinediones act via a different pathway than metformin, and the relationship between peroxisome proliferator-activated receptor agonists (PPARs), fatty-acid induced transcription factors associated with lipid metabolic disorders, and the innate immune system must be better explored.[61]

Patients who received combination anti-psoriatic drugs with metformin or pioglitazone were reported to have a significant decrease in CD4+ T cells, IL-2, C-reactive protein (CRP), ceruloplasmin, ALT, and AST levels. Interestingly, no significant changes in the fasting blood glucose levels, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides were identified, which raises the question regarding which biological marker has a direct versus peripheral relationship with psoriasis. El-Gharabawy et al's study of the mechanisms behind immunomodulating agents revealed that treatment groups who received both anti-psoriatic medication and pioglitazone had increased CD8+ levels while no significant changes in CD8+ were seen in patients treated with anti-psoriatic medication alone or with metformin alone, which contradicts the paradigm regarding the major effector role that Th1/CD8+ plays in the development of psoriasis.[3] Furthermore, treatment groups receiving either pioglitazone or metformin experienced an overall significant decrease in CD4+, which are involved in the initiation and maintenance of the pathogenic role of psoriasis.[62]

Metformin for Acanthosis Nigricans

Longer duration of therapy (>6 months), higher metformin dosages (1,700–2,000mg), and lower baseline weight of patients associated with higher efficacy for the treatment of AN. Factors associated with low efficacy of acanthosis nigricans included low dosages of metformin, slow titration of the metformin, and shorter treatment course, suggesting that more aggressive course of metformin therapy is preferred for treating AN. Studies reviewed suggests that the role of metformin in the treatment of AN involves interactions beyond weight and insulin sensitivity. The activation of insulin like growth factors by increased circulating insulin leading to keratinocyte and dermal fibroblast proliferation in overweight individuals represents an oversimplified and incomplete explanation regarding the role of metformin for the treatment of AN.

For example, while both metformin and rosiglitazone demonstrated skin texture improvement, only rosiglitazone led to quantifiable decrease in insulin levels. Additionally, Wasniewska et al.'s treatment of AN in an adolescent with normal weight suggests the role of metformin in non-obesity associated inflammatory reactions. Some studies even suggest that there is no statistically significant difference in the pro-inflammatory profile (TNF-α, IL-6 and adiponectin) between obese and non-obese patients with metabolic syndrome. Whether proinflammatory reactors (TNF-α, IL-6 and adiponectin) have a role in the pathogenesis of AN raises the further question regarding our understanding how metformin works.

While topical and oral retinoids are generally accepted to positively benefit patients with AN due to their keratolytic effect, Walling et al's study warrants further exploration of the synergy between isotretinoin and metformin. It should be noted that of the metformin non-responders reported by Verma et al. and Lee et al, one patient was pubertal with hyperinsulinemia and concomitant weight gain while the other had aromatase deficiency.[63,64] Aromatase deficiency can result in an inability to reverse insulin resistance and therefore may explain metformin's lack of efficacy.

Metformin for Acne

Fourteen of seventeen studies reviewed reported that metformin led to clinically significant improvement in PCOS-related acne. Of note, treating non-PCOS related acne with metformin remains controversial. One study involving men with refractory acne after treatment with oral metformin (dose range, 1000 to 2550mg/day) also showed positive results, however, these results may have been confounded by the initiation of low glycemic diets ($P<0.05$). A low sample size (n=20) and lack of stratification also calls for further follow-up studies.

Compared to OCPs, aggressive metformin treatment regimens (1700–2000mg/day) resulted in greater reduction of acne as well as menstrual irregularity compared to oral contraceptives. This suggests that metformin's role in disrupting the pathophysiology of acne should be better scrutinized and differentiated between patients with and without PCOS.[65,66]

Understanding the role of metformin in the treatment of PCOS-related acne raises the question whether metformin would achieve similar efficacy in non-PCOS patients. Metformin is theorized to decreases the follicular hyper-keratinization of cells overlying hair follicles through decreasing IGF-1 levels associated with insulin resistance, inflammatory markers (IFNg, IL-1, IL-8, andTNFa) associated with obesity and *Propionibacterium acnes*, and excess testosterone responsible for stimulating sebaceous oil production.[27]

Metformin for Hirsutism

Of the total of 46 studies investigated metformin's efficacy for hirsutism treatment in females with PCOS, 31 reported an improvement of hirsutism with metformin treatment, particularly a higher dose (>1500mg/day). Metformin treatment failure in patients with acne and hirsutism was once again noted using shorter treatment durations and insufficient control of the underlying metabolic disease.

Metformin's anti-androgenic effect may explain its efficacy in the treatment of hirsutism, which results from elevated circulating androgens (testosterone, dihydrotestosterone (DHT), and androstenedione) in women with PCOS. The 5-alpha reductase type 2 isoenzyme concentrated in the outer root sheath of hair follicles predominantly in the beard and genital hair DHT causes terminalization of the vellus hair and prolongs the anagen phase resulting in longer thicker hair. Metformin reduces the amount of free testosterone available for conversion into DHT.

It is important to differentiate the pathophysiology of PCOS-related hirsutism from idiopathic hirsutism before speculating the role that metformin plays. Mohammed et al's study (n=85) comparing patients with PCOS-related, idiopathic, and idiopathic hirsutism discovered that there is a significant inverse correlation between testosterone and omentin-1, a biomarker speculated to be involved in the development of non-PCOS related hirsutism.

Tolerability and Adverse Effects of Metformin

Metformin is generally well-tolerated by most patients, with mild-to-moderate short-term gastrointestinal upset cited as the most common side effect, albeit no incidences of lactic acidosis or severe hypoglycemia were reported. There was one isolated case of anemia reported by Singh and Bhansali was considered l, and a few reported cases of hyperpigmentation speculated to be associated with the patients' insulin resistance state.[5] Metformin is rarely prescribed by dermatologists due to the prevailing notion that its use falls within the realm of primary providers or endocrinologists, as well as concerns regarding side effects. However, dermatologists should more frequently consider metformin as an adjunct therapy given its promising results combined with its good tolerability.

CONCLUSION

High-dose and long-term therapy (>6 months) ranging from 1,000–2,000mg metformin/day has demonstrated promising efficacy in the treatment of psoriasis, HS and PCOS-related acne. This efficacy may be attributed to the anti-inflammatory effect of the drug at high systemic levels. Patients generally tolerate metformin well, which should provide reassurance for dermatologists to consider the addition of this adjunctive therapy. The treatment of PCOS related AN and hirsutism may require a more aggressive, and sustained course (>6 months) of metformin treatment regimen (starting and maintenance dose upwards of 1500mg). Metformin is safe and efficacious to use as an adjunct to oral contraceptives, statins, vitamin D, retinoids, and other first line treatments for psoriasis, HS, and PCOS, however, should not be used in conjunction with other insulin-lowering agents without close monitoring by endocrine specialist. However, limited and mixed results warrant further research regarding metformin's application for acanthosis nigricans and hirsutism to determine whether at higher doses may be more effective in patients with for both obese and non-obese female patients with PCOS.

DISCLOSURES

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