Dermatologic Implications of Glycemic Control Medications for Patients with Type 2 Diabetes Mellitus

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PRACTICE **POINTS**

- Type 2 diabetes mellitus (T2DM) is highly prevalent in patients with various dermatologic conditions; therefore, it is important for dermatologists to understand the adverse effects of T2DM medications to optimize treatment strategies.
- In addition to glycemic control and management, the hormonal and immunologic effects of T2DM medications can be leveraged to treat dermatologic conditions, particularly those associated with metabolic dysregulation.

Type 2 diabetes mellitus (T2DM) is a chronic disease with a rising prevalence worldwide that is characterized by hyperglycemia and insulin resistance. Metformin, which improves blood glucose levels and insulin sensitivity, is considered the first-line therapy for T2DM. In patients with T2DM who are overweight or obese, glucagonlike peptide 1 (GLP-1) and dual GLP-1/gastric inhibitory peptide (GIP) agonists are used as adjunct or alternative therapies given their dual benefits for insulin sensitivity and weight loss. Beyond the metabolic implications of T2DM medications, these agents also have hormonal and immunologic effects that may impact dermatologic diseases (eg, psoriasis, hidradenitis suppurativa [HS]). In this review, we highlight the dermatologic adverse effects and potential therapeutic benefits of metformin as well as GLP-1 and GLP-1/GIP agonists.

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by uncontrolled hyperglycemia. Over the past few decades, its prevalence has steadily increased, now affecting approximately 10% of adults worldwide and ranking among the top 10 leading causes of death globally.[1] The pathophysiology of T2DM involves persistent hyperglycemia that drives insulin resistance and a progressive decline in insulin production from the pancreas.[2] Medical management of this condition aims to reduce blood glucose levels or enhance insulin production and sensitivity. Aside from lifestyle modifications, metformin is considered the first-line treatment for glycemic control according to the 2023 American Association of Clinical Endocrinology's T2DM management algorithm.[3] These updated guidelines stratify adjunct treatments by individualized glycemic targets and patient needs. For patients who are overweight or obese, glucagonlike peptide 1 (GLP-1) and dual GLP-1/gastric inhibitory polypeptide (GIP) agonists are the preferred adjunct or second-line treatments.[3]

In this review, we highlight the dermatologic adverse effects and potential therapeutic benefits of metformin as well as GLP-1 and GLP-1/GIP agonists.

METFORMIN

Metformin is a biguanide agent used as a first-line treatment for T2DM because of its ability to reduce hepatic glucose production and increase peripheral tissue glucose uptake.[4] In addition to its effects on glucose, metformin has been shown to have anti-inflammatory properties via inhibition of the nuclear factor κB and mammalian target of rapamycin (mTOR) pathways, leading to decreased production of cytokines associated with T helper (Th) 1 and Th17 cell responses, such as IL-17, interferon gamma (IFN-γ), and tumor necrosis factor α (TNF-α).[5-7] These findings have spurred interest among clinicians in the potential use of metformin for inflammatory conditions, including dermatologic diseases such as psoriasis and hidradenitis suppurativa (HS).[8]

Adverse Effects

Metformin is administered orally and generally is well tolerated. The most common adverse effects include gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain.[9] While cutaneous adverse effects are rare, multiple dermatologic adverse reactions to metformin have been reported,[10,11] including leukocytoclastic vasculitis,[11-13]

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fixed drug eruptions,[14-17] drug rash with eosinophilia and systemic symptoms (DRESS) syndrome,[18] and photosensitivity reactions.[19] Leukocytoclastic vasculitis and DRESS syndrome typically develop within the first month following metformin initiation, while fixed drug eruption and photosensitivity reactions have more variable timing, occurring weeks to years after treatment initiation.[12-19]

Dermatologic Implications

Acanthosis Nigricans—Acanthosis nigricans (AN) is characterized by hyperpigmentation and velvety skin thickening, typically in intertriginous areas such as the back of the neck, axillae, and groin.[20] It commonly is associated with insulin resistance and obesity.[21-23] Treatments for AN primarily center around insulin sensitivity and weight loss,[24,25] with some benefit observed from the use of keratolytic agents.[26,27] Metformin may have utility in treating AN through its effects on insulin sensitivity and glycemic control. Multiple case reports have noted marked improvements in AN in patients with and without obesity with the addition of metformin to their existing treatment regimens in doses ranging from 500 mg to 1700 mg daily.[28-30] However, an unblinded randomized controlled trial (RCT) comparing the efficacy of metformin (500 mg 3 times daily) with rosiglitazone (4 mg/d), another T2DM medication, on AN neck lesions in patients who were overweight and obese found no significant effects in lesion severity and only modest improvements in skin texture in both groups at 12 weeks following treatment initiation.[31] Another RCT comparing metformin (500 mg twice daily) with a twice-daily capsule containing α-lipoic acid, biotin, chromium polynicotinate, and zinc sulfate, showed significant ($P<.001$) improvements in AN neck lesions in both groups after 12 weeks.[32] According to Sung et al,[8] longer duration of therapy (>6 months), higher doses (1700–2000 mg), and lower baseline weight were associated with higher efficacy of metformin for treatment of AN. Overall, the use of metformin as an adjunct treatment for AN, particularly in patients with underlying hyperglycemia, is supported in the literature, but further studies are needed to clarify dosing, duration of therapy, and patient populations that will benefit most from adding metformin to their treatment regimens.

Hirsutism—Hirsutism, which is characterized by excessive hair growth in androgen-dependent areas, can be challenging to treat. Metformin has been shown to reduce circulating insulin, luteinizing hormone, androstenedione, and testosterone, thus improving underlying hyperandrogenism, particularly in patients with polycystic ovary syndrome (PCOS).[33-35] Although single studies evaluating the efficacy of metformin for treatment of hirsutism in patients with PCOS have shown potential benefits,[36-38] meta-analyses showed no significant effects of metformin compared to placebo or oral contraceptives and decreased benefits compared to spironolactone and flutamide.[39] Given these findings showing that metformin was no more effective than placebo or other treatments, the current Endocrine Society guidelines recommend against the use of metformin for hirsutism.[39,40] There may be a role for metformin as an adjuvant therapy in certain populations (eg, patients with comorbid T2DM), although further studies stratifying risk factors such as body mass index and age are needed.[41]

Hidradenitis Suppurativa—Hidradenitis suppurativa is a follicular occlusive disease characterized by recurrent inflamed nodules leading to chronic dermal abscesses, fibrosis, and sinus tract formation primarily in intertriginous areas such as the axillae and groin.[42] Medical management depends on disease severity but usually involves antibiotic treatment with adjunct therapies such as oral contraceptives, antiandrogenic medications (eg, spironolactone), biologic medications, and metformin.[42] Preclinical and clinical data suggest that metformin can impact HS through metabolic and immunomodulatory mechanisms.[5,42] Like many chronic inflammatory disorders, HS is associated with metabolic syndrome.[43,44] A study evaluating insulin secretion after oral glucose tolerance testing showed increased insulin levels in patients with HS compared to controls ($P=.02$), with 60% (6/10) of patients with HS meeting criteria for insulin resistance. In addition, serum insulin levels in insulin-resistant patients with HS correlated with increased lesional skin mTOR gene expression at 30 ($r=.80$) and 60 ($r=1.00$) minutes, and mTOR was found to be upregulated in lesional and extralesional skin in patients with HS compared to healthy controls ($P<.01$).[45] Insulin activates mTOR signaling, which mediates cell growth and survival, among other processes.[46] Thus, metformin's ability to increase insulin sensitivity and inhibit mTOR signaling could be beneficial in the setting of HS. Additionally, insulin and insulinlike growth factor 1 (IGF-1) increase androgen signaling, a process that has been implicated in HS.[47]

Metformin also may impact HS through its effects on testosterone and other hormones.[48] A study evaluating peripheral blood mononuclear cells in patients with HS showed reduced IL-17, IFN-γ, TNF-α, and IL-6 levels in patients who were taking metformin (dose not reported) for longer than 6 months compared to patients who were not on metformin. Further analysis of ex vivo HS lesions cultured with metformin showed decreased IL-17, IFN-γ, TNF-α, and IL-8 expression in tissue, suggesting an anti-inflammatory role of metformin in HS.[5]

Although there are no known RCTs assessing the efficacy of metformin in HS, existing clinical data are supportive of the use of metformin for refractory HS.[49] Following a case report describing a patient with T2DM and stable HS while on metformin,[50] several cohort studies have assessed the efficacy of metformin for the treatment of HS. A prospective study evaluating the efficacy of metformin monotherapy (starting dose of 500 mg/d, titrated to 500 mg 3 times daily) in patients with and without T2DM with HS refractory to other therapies found clinical improvement in 72% (18/25) of patients using the Sartorius Hidradenitis Suppurativa Score, improving from a mean (SD) score of 34.40 (12.46) to 26.76 (11.22) at 12 weeks ($P=.0055$,) and 22.39 (11.30) at 24 weeks ($P=.0001$).

Additionally, 64% (16/25) of patients showed improved quality of life as evaluated by the Dermatology Life Quality Index (DLQI), which decreased from a mean (SD) score of 15.00 (4.96) to 10.08 (5.96)(P=.0017) at 12 weeks and 7.65 (7.12)(P=.000009) at 24 weeks on treatment.[48] In a retrospective study of 53 patients with HS taking metformin started at 500 mg daily and increased to 500 mg twice daily after 2 weeks (when tolerated), 68% (36/53) showed some clinical response, with 19% (7/36) of those patients having achieved complete response to metformin monotherapy (defined as no active HS).[51] Similarly, a retrospective study of pediatric patients with HS evaluating metformin (doses ranging from 500-2000 mg daily) as an adjunct therapy described a subset of patients with decreased frequency of HS flares with metformin.[52] These studies emphasize the safety profile of metformin and support its current use as an adjunctive therapy for HS.

Acne Vulgaris—Acne vulgaris (AV) is a chronic inflammatory disorder affecting the pilosebaceous follicles.[11] Similar to HS, AV has metabolic and hormonal influences that can be targeted by metformin.[53] In AV, androgens lead to increased sebum production by binding to androgen receptors on sebocytes, which in turn attracts *Cutibacterium acnes* and promotes hyperkeratinization, inducing inflammation.[54] Thus, the antiandrogenic effects of metformin may be beneficial for treatment of AV. Additionally, sebocytes express receptors for insulin and IGF-1, which can increase the size and number of sebocytes, as well as promote lipogenesis and inflammatory response, influencing sebum production.[54] Serum levels for IGF-1 have been observed to be increased in patients with AV[55] and reduced by metformin.[56] A recent meta-analysis assessing the efficacy of metformin on AV indicated that 87% (13/15) of studies noted disease improvement on metformin, with 47% (7/15) of studies showing statistically significant (P<0.05) decreases in acne severity.[57] Although most studies showed improvement, 47% (7/15) did not find significant differences between metformin and other interventions, indicating the availability of comparable treatment options. Overall, there has been a positive association between metformin use and acne improvement.[57] However, it is important to note that most studies have focused on females with PCOS,[57] and the main benefits of metformin in acne might be seen when managing comorbid conditions, particularly those associated with metabolic dysregulation and insulin resistance. Further studies are needed to determine the generalizability of prior results.

Psoriasis—Psoriasis is a chronic autoinflammatory disease characterized by epidermal hyperplasia with multiple cutaneous manifestations and potential for multiorgan involvement. Comorbid conditions include psoriatic arthritis, metabolic syndrome, and cardiovascular disease.[58] Current treatment options depend on several factors (eg, disease severity, location of cutaneous lesions, comorbidities) and include topical, systemic, and phototherapy options, many of which target the immune system.[58,59] A meta-analysis of 3 RCTs showed that metformin (500 mg/d or 1000 mg/d) was associated with significantly improved Psoriasis Area and Severity Index (PASI) 75% reductions (odds ratio [OR], 22.02; 95% CI, 2.12-228.49; P=.01) and 75% reductions in erythema, scaling, and induration (OR, 9.12; 95% CI, 2.13-39.02; P=.003) compared to placebo.[60] In addition, an RCT evaluating the efficacy of metformin (1000 mg/d) or pioglitazone (30 mg/d) for 12 weeks in patients with psoriasis with metabolic syndrome found significant improvements in PASI75 (P=.001) and erythema, scaling, and induration (P=.016) scores as well as in Physician Global Assessment scores (P=.012) compared to placebo and no differences compared to pioglitazone.[61] While current psoriasis management guidelines do not include metformin, its use may be worth consideration as an adjunct therapy in patients with psoriasis and comorbidities such as T2DM and metabolic syndrome.[59] Metformin's potential benefits in psoriasis may lie outside its metabolic influences and occur secondary to its immunomodulatory effects, including targeting of the Th17 axis or cytokine-specific pathways such as TNF-α, which are known to be involved in psoriasis pathogenesis.[58]

Central Centrifugal Cicatricial Alopecia—Central centrifugal cicatricial alopecia (CCCA) is a form of scarring alopecia characterized by chronic inflammation leading to permanent loss of hair follicles on the crown of the scalp.[62] Current treatments include topical and intralesional corticosteroids, as well as oral antibiotics. In addition, therapies including the antimalarial hydroxychloroquine and immunosuppressants mycophenolate and cyclosporine are used in refractory disease.[63,64] A case report described 2 patients with hair regrowth after 4 and 6 months of treatment with topical metformin 10% compounded in a proprietary transdermal vehicle.[65] The authors speculated that metformin's effects on CCCA could be attributed to its known agonistic effects on the adenosine monophosphate-activated protein kinase (AMPK) pathway with subsequent reduction in inflammation-induced fibrosis.[65,66] Microarray[67] and proteomic[68] analysis have shown that AMPK is known to be downregulated in CCCA , making it an interesting therapeutic target in this disease. A recent retrospective case series demonstrated that 67% (8/12) of patients with refractory CCCA had symptomatic improvement, and 50% (6/12) showed hair regrowth after 6 months of low-dose (500 mg/d) oral metformin treatment.[62] In addition, metformin therapy showed antifibrotic and anti-inflammatory effects when comparing scalp biopsies before and after treatment. Results showed decreased expression of fibrosis-related genes (matrix metalloproteinase 7, collagen type IV α 1 chain), and gene set variation analysis showing reduced Th17 (P=.04) and increased AMPK signaling (P=.02) gene set expression.[62] These findings are consistent with previous studies describing the upregulation of AMPK[66] and downregulation of Th17[6] following metformin treatment. The immunomodulatory effects of metformin could be attributed to AMPK-mediated mTOR and NF-κB downregulation,[62] although more studies are needed to understand these mechanisms and further explore the use of metformin in CCCA.

Skin Cancer—Metformin also has been evaluated in the setting of skin malignancies, including melanoma, squamous cell carcinoma, and basal cell carcinoma. Preclinical data suggest that metformin decreases cell viability in tumors through interactions with pathways involved in proinflammatory and prosurvival mechanisms such as NF-κB and mTOR.[69,70] Additionally, given metformin's inhibitory effects on oxidative phosphorylation, it has been postulated that it could be used to overcome treatment resistance driven by metabolic reprogramming.[71,72] Most studies related to metformin and skin malignancies are still in preclinical stages; however, a meta-analysis of RCTs and cohort studies did not find significant associations between metformin use and skin cancer risk, although data trended toward a modest reduction in skin cancer among metformin users.[73] A retrospective cohort study of melanoma in patients with T2DM taking metformin (250-2000 mg/d) found that the 5-year incidence of recurrence was lower in the metformin cohort compared to nonusers (43.8% vs 58.2%, respectively)(P=.002), and overall survival rates trended upward in the higher body mass index (>30) and melanoma stages 1 and 2 groups but did not reach statistical significance.[74] In addition, a whole population case-control study in Iceland reported that metformin use at least 2 years before first-time basal cell carcinoma diagnosis was associated with a lower risk for disease (adjusted OR, 0.71; 95% CI, 0.61-0.83) with no significant dose-dependent differences; there were no notable effects on squamous cell carcinoma risk.[75] Further preclinical and clinical data are needed to elucidate metformin's effects on skin malignancies.

GLP-1 AND DUAL GLP-1/GIP AGONISTS

Glucagonlike peptide 1 and dual GLP-1/GIP agonists are emerging classes of medications currently approved as adjunct and second-line therapies for T2DM, particularly in patients who are overweight or obese as well as in those who are at risk for hypoglycemia.[3] Currently approved GLP-1 agonists for T2DM include semaglutide, dulaglutide, exenatide, liraglutide, and lixisenatide, while tirzepatide is the only approved dual GLP-1/GIP agonist. Activating GLP-1 and GIP receptors stimulates insulin secretion and decreases glucagon production by the pancreas, thereby reducing blood glucose levels. Additionally, some of these medications are approved for obesity given their effects in delayed gastric emptying and increased satiety, among other factors.

Over the past few years, multiple case reports have described the associations between GLP-1 agonist use and improvement of dermatologic conditions, particularly those associated with T2DM and obesity, including HS and psoriasis.[76,77] The mechanisms through which this occurs are not fully elucidated, although basic science and clinical studies have shown that GLP-1 agonists have immunomodulatory effects by reducing proinflammatory cytokines and altering immune cell populations.[77-80] The numerous ongoing clinical trials and research studies will help further elucidate their benefits in other disease settings.[81]

Adverse Reactions

Most GLP-1 and GLP-1/GIP agonists are administered subcutaneously, and the most commonly reported cutaneous adverse effects are injection site reactions.[82] Anaphylactic reactions to these medications also have been reported, although it is unclear if these were specific to the active ingredients or to injection excipients.[83,84] A review of 33 cases of cutaneous reactions to GLP-1 agonists reported 11 (33%) dermal hypersensitivity reactions occurring as early as 4 weeks and as late as 3 years after treatment initiation. It also described 10 (30%) cases of eosinophilic panniculitis that developed within 3 weeks to 5 months of GLP-1 treatment, 3 (9%) cases of bullous pemphigoid that occurred within the first 2 months, 2 (6%) morbilliform drug eruptions that occurred within 5 weeks, 2 (6%) cases of angioedema that occurred 15 minutes to 2 weeks after treatment initiation, and 7 (21%) other isolated cutaneous reactions. Extended-release exenatide had the most reported reactions followed by liraglutide and subcutaneous semaglutide.[85]

In a different study, semaglutide use was most commonly associated with injection site reactions followed by alopecia, especially with oral administration. Unique cases of angioedema (2 days after injection), cutaneous hypersensitivity (within 10 months on treatment), bullous pemphigoid (within 2 months on treatment), eosinophilic fasciitis (within 2 weeks on treatment), and leukocytoclastic vasculitis (unclear timing), most of which resolved after discontinuation, also were reported.[86] A recent case report linked semaglutide (0.5 mg/wk) to a case of drug-induced systemic lupus erythematosus that developed within 3 months of treatment initiation and described systemic lupus erythematosus–like symptoms in a subset of patients using this medication, namely females older than 60 years, within the first month of treatment.[87] Hyperhidrosis was listed as a common adverse event in exenatide clinical trials, and various cases of panniculitis with exenatide use have been reported.[82,88] Alopecia, mainly attributed to accelerated telogen effluvium secondary to rapid weight loss, also has been reported, although hair loss is not officially listed as an adverse effect of GLP-1 agonists, and reports are highly variable.[89] Also secondary to weight loss, facial changes including sunken eyes, development of wrinkles, sagging jowls around the neck and jaw, and a hollowed appearance, among others, are recognized as undesirable adverse effects.[90] Mansour et al[90] described the potential challenges and considerations to these rising concerns associated with GLP1-agonist use.

Dermatologic Implications

Hidradenitis Suppurativa—Weight loss commonly is recommended as a lifestyle modification in the management of HS. Multiple reports have described clinical improvement of HS following weight loss with other medical interventions, such as dietary measures and bariatric surgery.[91-94] Thus, it has been postulated that medically supported weight loss with GLP-1 agonists can help improve HS[95]; however, the data on the effectiveness of GLP-1 agonists on HS are still scarce and

mostly have been reported in individual patients. One case report described a patient with improvements in their recalcitrant HS and DLQI score following weight loss on liraglutide (initial dose of 0.6 mg/d, titrated to 1.8 mg/d).[76] In addition, a recent case report described improvements in HS and DLQI score following concomitant tirzepatide (initial dose of 2.5 mg/0.5 mL weekly, titrated to 7.5 mg/0.5 mL weekly) and infliximab treatment.[96] The off-label use of these medications for HS is debated, and further studies regarding the benefits of GLP-1 agonists on HS still are needed.

Psoriasis—Similarly, several case reports have commented on the effects of GLP-1 agonists on psoriasis.[97,98] An early study found GLP-1 receptors were expressed in psoriasis plaques but not in healthy skin and discussed that this could be due to immune infiltration in the plaques, providing a potential rationale for using anti-inflammatory GLP-1 agonists for psoriasis.[99] Two prospective cohort studies observed improvements in PASI and DLQI scores in patients with psoriasis and T2DM after liraglutide treatment and noted important changes in immune cell populations.[80,100] A recent RCT also found improvements in DLQI and PASI scores ($P<.05$) in patients with T2DM following liraglutide (1.8 mg/d) treatment, along with overall decreases in inflammatory cytokines, such as IL-23, IL-17, and TNF-α.[77] However, another RCT in patients with obesity did not observe significant improvements in PASI and DLQI scores compared to placebo after 8 weeks of liraglutide (initial dose of 0.6 mg/d, titrated to 1.8 mg/d) treatment.[99] Although these results could have been influenced by the short length of treatment compared to other studies, which observed participants for more than 10 weeks, they highlight the need for tailored studies considering the different comorbidities to identify patients who could benefit the most from these therapies.

Alopecia—Although some studies have reported increased rates of alopecia following GLP-1 agonist treatment, others have speculated about the potential role of these medications in treating hair loss through improved insulin sensitivity and scalp blood flow.[86,89] For example, a case report described a patient with improvement in androgenetic alopecia within 6 months of tirzepatide monotherapy at 2.5 mg weekly for the first 3 months followed by an increased dose of 5 mg weekly.[101] The authors described the role of insulin in increasing dihydrotestosterone levels, which leads to miniaturization of the dermal papilla of hair follicles and argued that improvement of insulin resistance could benefit hair loss. Further studies can help elucidate the role of these medications on alopecia.

FINAL THOUGHTS

Standard T2DM treatments including metformin and GLP-1 and GLP-1/GIP agonists exhibit metabolic, immunologic, and hormonal effects that should be explored in other disease contexts. We reviewed the current data on T2DM medications in dermatologic conditions to highlight the need for additional studies to better understand the role that these medications play across diverse patient populations. Type 2 diabetes mellitus is a common comorbidity in dermatology patients, and understanding the multifactorial effects of these medications can help optimize treatment strategies, especially in patients with coexisting dermatologic and metabolic diseases.

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