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SHORT REVIEW

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Novel Metformin Indications and Skin Disorders

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Abstract

Metformin is the first-line medication to increase insulin sensitivity in insulin-resistant conditions such as type 2 diabetes, polycystic ovary syndrome, and obesity. However, metformin is a drug with a wide range of pharmacological properties, showing the ability to treat various skin conditions. Some inflammatory skin dermatoses, skin neoplasms, endocrinology-related dermatosis, pigmentary disorders, skin aging, and wound healing have all shown improvement when metformin is used. This review discusses the most recent research supporting the use of metformin as a treatment for common skin conditions.(**International Journal of Biomedicine. 2022;12(4):521-525.**).

Keywords: Metformin • indications • skin disorders

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Abbreviations

AMPK, AMP-activated protein kinase; **AN**, acanthosis nigricans; **BP-like EBA**, bullous pemphigoid-like epidermolysis bullous acquisita; **GLUT4**, glucose transporter 4; **HS**, hidradenitis suppurativa; **IR**, insulin resistance; **IGF-1**, insulin growth factor-1; **IPL**, intense pulsed light; **MITF**, microphthalmia-associated transcription factor; **OCT**, organic cation transporter; **PPARγ**, peroxisome proliferator-activated receptor γ; **PCOS**, polycystic ovary syndrome; **PKC**, protein kinase C; **T2D**, type 2 diabetes; **TRP**, tyrosinase-related protein.

Introduction

Hyperandrogenism associated with hyperinsulinemia and insulin resistance (IR) may have a significant impact on the onset of several dermatological conditions.(1) IR is defined by decreased cellular glucose absorption and average or increased insulin levels. The cytoplasmic fraction of insulin-responsive glucose transporter 4 (GLUT4) is significantly decreased in IR. Metformin counteracts this action by slowing GLUT4 endocytosis and raising GLUT4 gene expression, resulting in enhanced glucose absorption and decreased IR. Metformin may lower both fasting and induced plasma insulin levels, with this activity mediated by interactions with PPARγ.(2) It reduces blood glucose primarily by decreasing hepatic glucose production and boosting sensitivity to insulin through an AMPK-dependent mechanism.(3) Metformin is an important medicine for a variety of skin disorders. This article will look at metformin from a dermatological standpoint.

Metformin's oral bioavailability ranges between 40% and 60%. Complete gastrointestinal absorption occurs within 6 hours following medication administration. Plasma membrane

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monoamine transporter mediates gastrointestinal absorption.[4] Metformin is not metabolized, and its half-life is 5 hours. OCT-1 and OCT-3 aid in metformin hepatic absorption, while OCT-2 aids in metformin uptake from the bloodstream into kidney epithelial cells. Metformin is eliminated from the body by active renal excretion.[5]

Metformin and Inflammatory Dermatoses

Acne management

Acne is a relatively prevalent chronic inflammatory skin condition that affects the folliculopilosebaceous unit. Acne vulgaris affects 85% of adolescents. The pathophysiology of acne vulgaris is complex; excessive sebum, improper follicular keratinization, colonization of cutibacterium acne, and inflammation are all implicated.[6] Comedones, inflammatory papules, pustules, and cysts are characteristic lesions that may cause scarring and pigmentation changes. Typically, acne lesions are situated on the face, shoulders, back, and chest and are classified into 3 types based on the severity of the disease: mild, medium, and severe.[7] Acne development is also influenced by abnormal hormone function, hyperandrogenemia, hyperinsulinemia, and increased IGF-1. The activation of IGF-1 receptors by hyperinsulinemia is responsible for the enhanced proliferation and malfunctioning of keratinocytes. IGF-1 hypersecretion results in aberrant sebum production, sebocyte hyperproliferation, and lipogenesis.[1] Insulin and IGF-1 facilitate the production of androgens. IGF-1 also improves androgen receptor signal transduction. As a result, the increased testosterone level promotes hyperseborrhea.[8] Some investigations have indicated that hyperinsulinemia, and not elevated testosterone levels, may have been the only cause of acne.[9] According to Kartal et al.,[10] IR is a risk factor for acne that is independent of hyperandrogenemia.

Hyperinsulinemia may play a significant role in acne pathogenesis by promoting hyperandrogenemia.[11] The PPAR ligands mediate the action of androgens on sebaceous lipids. Increased PPARγ activity suppresses the GLUT4 promoter, resulting in increased IR. Metformin increases glucose absorption and improves IR via slowing GLUT4 endocytosis and raising GLUT4 expression of genes. Metformin could reduce plasma insulin and IR through PPAR interaction.[12] There are 3 PPAR isotypes: α, δ, and γ. PPARα and PPARγ predominate in human sebocytes. PPARs are found in sebocyte mitochondria, peroxisomes, and microsomes and control a variety of lipid metabolic genes.[13] IGF-1 increases acne formation by stimulating sebum hypersecretion. Metformin lowers elevated blood levels of IGF-1 and androgen in women with polycystic ovary syndrome (PCOS).[14] It may also restrict proinflammatory cytokine release and block monocyte differentiation, reducing inflammation.[15] Begin with a modest dosage of 250 mg, gradually raising it by 250 mg each week until the maximum dose of 1500-2000 mg is reached. For long-term success, a positive impact should be demonstrated within 6 months. Metformin is a safer acne treatment for women with hirsutism and acne caused by PCOS.[14]

Hidradenitis suppurativa

HS is essentially a pilosebaceous unit condition accompanied by an abnormality in hair structure, with apocrine gland participation becoming a minor feature.[16] Genetic factors linked to HS cause enlargement and deformation of the upper section of the follicle infundibulum, followed by obstruction and eventual burst, re-epithelialization, sinus tract creation, bacterial invasion, pustule, and fistula. HS has also been linked to PCOS, and with a decrease in symptoms after menopause, a link to hormonal impacts is also proposed.[16]

Metformin might be considered a viable therapy option in this situation due to the prevalence of poor glucose tolerance in a significant percentage of these individuals. Metformin works in HS via an unknown mechanism. It has been proposed, however, that metformin functions primarily via impairing androgen action, with a probable impact on gene expression implicated in this syndrome. Secondly, it enhances glucose consumption by improving the sensitivity of receptors, resulting in less IR. In pilot research, Verdolini et al.[17] established metformin's effectiveness in treating resistant HS. The treatment was maintained for 24 weeks. The dermatology life quality index improved, and the change was considerable (64%).

Psoriasis

Psoriasis is a persistent inflammatory skin disorder that develops erythematous scaly plaques.[18] Psoriasis is now considered a systemic illness. It is often linked to obesity, metabolic syndrome, and T2D.[19] Metformin works on and stimulates the enzyme AMP-activated protein kinase (AMPK). Once active, this enzyme has been found to inhibit the function of macrophages, endothelial cells, T-lymphocytes, dendritic cells, and monocytes, resulting in anti-inflammatory responses. Metformin also possesses anti-inflammatory effects that are not reliant on AMPK.[19] Metformin inhibits the generation of reactive oxygen species by complex I (NADH-ubiquinone reductase) suppression in the inner mitochondrial membrane and may significantly change T-cell responses.[20,21] Cytokines and inflammatory markers like IFN-γ, TNF-α, and C-reactive protein have been shown to decrease in response to metformin administration.[22] Metformin has been demonstrated to suppress proliferation in keratinocytes by blocking the mitogen-activated protein kinase pathway.[23] Additionally, in human keratinocyte cultures, metformin reduced growth and proinflammatory cytokines through the rapamycin signaling pathway.[24] Further, metformin has been proven in experimental investigations to reduce liver toxicity associated with methotrexate, suggesting that it might be used in conjunction with methotrexate to manage psoriasis, making methotrexate use safer. Metformin's advantages for psoriasis are established most clearly in individuals with impaired sugar tolerance and/or metabolic syndrome.[25]

BP-like EBA

BP-like EBA is a granulocyte-mediated cutaneous condition caused by autoantibodies. Pemphigoid disorders are autoimmune blistering skin illnesses characterized by an immune reaction to dermal-epidermal adhesion complex proteins.[26] Autoantibody accumulation in the PD dermis attracts immune cells, notably granulocytes. Granulocytes tear down the dermal-epidermal adhesion complex by releasing ROS and proteases, causing subepidermal clefts that appear as erosions and blisters.[27]

Because neutrophil activation by immune complexes is the key effector phase step of BP-like EBA.[28] Metabolism-modulating agents such as metformin may have systemic

effects and decrease neutrophils, especially during ongoing immunological reactions.[29] In support of these ideas, the antidiabetic medication metformin reduces OxPhos via inhibiting mitochondrial complex I.[30] It has a much better safety profile and fewer adverse effects than the immunosuppressive medications now used to treat pemphigoid disorders.[31] Metformin also reduces corticosteroid side effects, making a combined treatment of corticosteroids and metformin an attractive possibility for treating pemphigoid disorders.[32] Metformin has a variety of pharmacological actions, and in vivo efficacy is probably the average of these activities. It stimulates Tregs and M2 macrophages while suppressing M1 macrophages, resulting in greater amounts of anti-inflammatory cytokines, notably IL-10.[33,34] Metformin therapy elevated IL-10 and TGF-β in lesional skin and enhanced Tregs. IL-10 and Tregs lower inflammation in BP-like EBA skin lesions; therefore, their elevated levels may have contributed to metformin's therapeutic benefits.[35] The number of macrophages in the infiltrate was decreased. Still, there was no transition from M1 to M2 macrophages, implying that the decrement in raw numbers of M1 macrophages may have been related to metformin's therapeutic benefits.[36]

Metformin and Skin Neoplasms

Metformin's significance in skin cancer chemoprevention has recently been hypothesized.[37] There is accumulating evidence that metformin can be used to treat melanoma and squamous cell carcinoma.[38,39]

Squamous Cell Carcinoma

Metformin's impact on squamous cell carcinoma chemoprevention is due to its enhancing action on AMPK, which suppress rapamycin signaling molecular target pathway. Recent research showed that metformin has an AMPK-independent activity as an anticancer drug.[40,41] Metformin also promotes apoptosis and elevates the Bax: Bcl-2 proportion in squamous cell carcinoma cells. Bcl-2 is an antiapoptotic protein, while Bax is a proapoptotic protein. As a result, this increase promotes tumor cell apoptosis.[42] Metformin also targets the nuclear factor-kappa-beta pathway and affects the PI3K/AK+ and ERK/p38 microtubule-associated protein kinase signaling pathways, reducing these pathways that are crucial for cellular multiplication and viability. Metformin has recently been discovered to have a function in suppressing the proliferation of cancer stem cells.[43] In addition to its anticancer actions, metformin has been demonstrated to enhance the effects of traditional chemotherapeutic drugs.[38]

Melanoma

Metformin increases p53 expression, which enhances anticancer signaling in melanoma.[39] In addition, metformin inhibits transcription factors Snail and Slug and reduces epithelial-mesenchymal conversion in melanoma and matrix metalloproteinase activity, boosting anti-invasive and antimetastatic actions. In recent research, Martin et al. found that metformin might promote the proliferation of $BRAF^{V600E}$-mutated melanoma cells in vitro by upregulating VEGF. When metformin was coupled with VEGF inhibitors, the development of these cancerous cells was inhibited in vivo. Considering these findings, it may be safe to assume that combining metformin and VEGF antagonists with BRAF mutant melanoma potentially resistant to BRAF inhibitors might be an effective alternative treatment.[44]

Endocrine-Related Dermatosis

Hirsutism

Hirsutism is described as the abnormal development of male-pattern hair on a woman's body. Lips, chin, and chest are examples of specific areas. There is an underlying PCOS in around 90% of hirsute females, or an underlying cause has not yet been identified. According to some claims, lowering circulating insulin levels lowers the amount of free testosterone in free circulation, suggesting that metformin may be useful in hirsutism management.[45]

Few studies have examined the effect of metformin on hirsutism as the primary objective. After a 14-month, double-blind, placebo-controlled randomized trial, Kelly and Gordon observed a slight decrease in the Ferriman-Gallwey score. In this research, metformin 500mg was delivered initially, followed by a 3-week progressive raise to 500 mg 3 times a day until the conclusion of therapy.[45] Ibáñez et al.[46] reported that metformin medication was successful in slowing the onset of hyperandrogenism, hirsutism, and PCOS in girls aged 8 to 12 years. Finally, a randomized controlled trial of 70 PCOS patients who had metformin plus intense pulsed light (IPL) for hair removal vs. IPL alone for 5 sessions over 6 months showed the metformin-IPL regimen was better.[47] However, until additional data is collected, metformin is not a first-line hirsutism therapy.

Acanthosis Nigricans

Acanthosis nigricans (AN) is a common skin disorder that is distinguished by black, coarse, thick, and velvety skin texture. Its distribution is generally bilateral, and it may be found in the axilla, neck, groin folds, antecubital and popliteal fossas, and a few other uncommon locations. A deficiency in glucose GLUT4 diffusion to the plasma membrane of myocytes and adipocytes may enhance IGF-R activity and so play a role in the pathogenesis of acanthosis nigricans.[48] The link between benign acanthosis nigricans and IR has recently been shown, and being overweight is a common co-morbidity in these individuals. Furthermore, obese AN people had higher insulin levels than obese persons without acanthosis nigricans.[49]

The pathophysiology of acanthosis nigricans is complicated, including the interaction of many receptors and growth factors. The activation of receptors from the tyrosine kinase family is involved in the development of acanthosis nigricans.[50,51] Metformin has positive benefits in acanthosis nigricans through preventing GLUT4 receptor endocytosis, permitting its movement to the plasma membrane, and so facilitating peripheral glucose consumption, reducing hyperinsulinemia, improving insulin sensitivity, and promoting body weight and reducing fat mass. In addition, the conjunction of metformin with glimepiride or thiazolidine may enhance its effect on acanthosis nigricans when metformin alone is ineffective.[52]

Disorders of Increased Pigmentation

Metformin's involvement in treating hyperpigmentation illnesses, particularly melasma, has just lately been explored. Metformin's positive impact has been related to several molecular pathways. Metformin inhibits the production of 3 melanogenic

proteins: tyrosinase, TRP-1, and TRP-2.[53] Metformin does this by first decreasing levels of cAMP, which inhibits protein kinase A activity. As a result, the expression of the MITF is reduced. MITF is a transcription factor known as the melanocyte viability master gene. Whenever its action is inhibited, transcription of numerous melanogenic proteins like TRP-1, tyrosinase, MART-1, TRP-2, and PKC- is reduced.[54] In addition, metformin suppresses the action of PKC-β. PKCβ activated by diacylglycerol (DAG) induces melanogenesis via the activation of tyrosinase. Metformin inhibits this activation conferred by DAG to PKC-β, resulting in a decrease in pigmentation.[55] However, this effect has been proven only by topical metformin and not by systemic administration of the medication.[56]

In conclusion, although metformin is typically used to treat T2D, it also has the potential to treat a variety of cutaneous conditions, particularly those associated with IR and hyperandrogenism. There have lately been encouraging studies about the use of metformin to treat inflammatory diseases, endocrine-related dermatosis, cutaneous cancers, and hyperpigmentation illnesses. Metformin could, therefore, have systemic and topical dermatological applications.

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Competing Interests

The authors declare that they have no competing interests.

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