

Metformin as an add-on to Methotrexate in Psoriasis Treatment: Review Article

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ABSTRACT

Background: Skin inflammation caused by the immune system that affects the extensor surfaces of the extremities, sacrum, and scalp is called psoriasis. It affects between 2% and 4% of the world's population. Several clinical subtypes exist. When it comes to impact less than 10% of the body surface area (BSA), it might be either localised or generalised. Obesity, diabetes mellitus, metabolic syndrome, and cardiovascular disease have been linked to it. The first-line anti-diabetic drug metformin is used to treat type 2 diabetes mellitus (T2DM) in addition to its favorable effects on lipid profiles, weight loss, cardiovascular risk, and hyperinsulinemia in those patients. When AMP-activated protein kinase (AMPK), an enzyme involved in the anti-inflammatory response, is activated, dendritic cells and T cells are reduced and T-cell activation is reduced as well, all of which lead to the inhibition of cell proliferation and the improvement of symptoms associated with the skin condition known as "psoriasis."

Objective: This review article aimed to assess the role of metformin as an adjuvant therapy to methotrexate in the treatment of generalized psoriasis.

Methods: The databases were searched for articles published in English in 3 data bases [PubMed – Google scholar - Science direct] and Boolean operators (and, or, not) had been used such as [Metformin or, methotrexate, metabolic syndrome and psoriasis] and in peer-reviewed articles between August 2003 and March 2021.

Conclusion: Metformin and methotrexate may enhance psoriasis patients' clinical results by improving metabolic syndrome parameters due to their antiproliferative and anti-inflammatory actions.

Keywords: Metformin, Methotrexate, Metabolic syndrome, Psoriasis.

INTRODUCTION

If you've ever wondered what causes psoriasis, you've come to the right place. Psoriasis pathogenesis can be caused by a variety of reasons including genetic, environmental, and immune-mediated factors ⁽¹⁾. Several clinical variants of psoriasis have been identified, with plaque-type psoriasis being the most common variant. Some of the methods used in the treatment of eczema include topical and systemic drugs as well as other adjuncts such as moisturizers and salicylic acid ⁽²⁾.

The review article aimed to assess the role of metformin as an adjuvant therapy to methotrexate in the treatment of generalized psoriasis.

METHODS

A search strategy has been performed to determine the related literature. Initially, the objective of review was identified to assess the role of metformin as an adjuvant therapy to methotrexate in the treatment of generalized psoriasis. Relevant keywords included metformin, methotrexate, metabolic syndrome and psoriasis, more synonymous key words had been used.

These databases were searched for articles published in English in 3 data bases [PubMed – Google scholar- science direct] and Boolean operators (AND, OR, NOT) had been used and in peer-reviewed articles between August 2003 and March 2021. A 18-year date range was selected, and selected data were filtered. However, the range of time interval for researches was wide as there was scarcity of data on the particular reviewed, accurate and depth in the retrieved literature.

Documents in a language apart from English have been excluded as sources for interpretation was not found. Papers apart from main scientific studies had been excluded (documents unavailable as total written text, conversation, conference abstract papers and dissertations).

Epidemiology:

Psoriasis prevalence varies widely among countries and regions, and it appears to be linked to factors such as climate and ancestry. Tropical regions and people with darker complexion tend to have less of it. Psoriasis affects around 2% to 3% of the general population around the world, according to the World Health Organization ⁽³⁾.

Age prevalence of psoriasis, it has a peak between the ages of 20-30 and 50-60 years. It is estimated that 10% to 15% of new cases occur in children younger than 10 years. When symptoms first appear, the average patient is 28 years old ⁽⁴⁾.

Methotrexate (MTX), a classic anti-psoriatic drug, is still extremely beneficial as a rescue medication or in combination with other systemic medications, such as biologics as a first-line treatment for psoriasis and psoriatic arthritis. It is widely used around the world ⁽⁵⁾.

Glucose intolerance, hypertension, dyslipidemia as well as obesity, are all risk factors for cardiovascular disease in the metabolic syndrome ⁽⁶⁾. Immune-mediated diseases, such as psoriasis, are known to raise the risk of other systemic illnesses. Psoriasis has been linked to a number of systemic disorders including cardiovascular disease, obesity, diabetes, high blood

pressure, and the metabolic syndrome, according to several studies ⁽⁷⁾.

The fact that immune-mediated diseases are often accompanied by metabolic problems underscores the critical role that the immune system plays in regulating metabolism ⁽⁸⁾. Systemic comorbidities may result from an interaction between the local cytokine network in psoriasis and distant organs, according to this hypothesis ⁽⁹⁾.

Metformin as an add-on therapy for psoriasis:

Biguanidine and metformin are herbal remedy first synthesized in 1922, and subsequently its properties as a "Glucophage" compound have been discovered. It has been widely used for the treatment of diabetes, being accessible, easy to administer, with few side effects, and with the potential to decrease body weight in obese patients ⁽¹⁰⁾.

Since 2009, metformin has been recommended for patients with type II diabetes as a first-line treatment, either as monotherapy or in combination with other anti-diabetic agents. Metformin does not cause hypoglycemia because the beta cells in the pancreas are not stimulated to secrete insulin, but it reduces serum glucose levels by inhibiting the synthesis of glucose in the liver and increasing the sensitivity of peripheral tissue to insulin ⁽¹¹⁾. Metformin also has a positive impact on diabetic patient's weight, which is critical. The lower blood glucose levels associated with metformin therapy have also been proven to minimize the incidence of myocardial infarction and arrhythmias in patients at high risk of cardiovascular problems ⁽¹²⁾.

Furthermore, several studies have investigated the efficacy of metformin in patients with type I diabetes. **Nadeau et al.** ⁽¹³⁾ reported a decrease in insulin dose, an improvement in body mass index, and a decrease in waist circumference, particularly in women. Moreover, improved heart failure outcomes and lower androgen levels have been reported in women with type I diabetes and hyperandrogenism after metformin administration ⁽¹⁴⁾.

The benefits of metformin in individuals with pre-diabetes have been demonstrated. **Capitaino et al.** ⁽¹⁵⁾ observed a reduced risk of type II diabetes by 31% and a reduction of body weight by an average of 2 kg following metformin administration.

In addition, it seems to have other applications in dermatology. Metformin has been successfully used for the treatment of several skin diseases, including acanthosis nigricans, acne, hyperpigmentation, eruptive xanthomas, hidradenitis suppurativa, hirsutism, squamous cell carcinoma, and melanoma ⁽¹⁶⁾.

Metformin in psoriasis patients:

Because many psoriasis patients also have metabolic syndrome, **Singh and Bhansali** ⁽¹⁷⁾ studied the effects of daily 1 g metformin on the metabolic syndrome in psoriasis patients. A marked improvement in the metabolic syndrome was observed following metformin administration compared to placebo (P =

0.046). The proven efficacy of metformin on the metabolic syndrome is a potential axis for improving psoriasis. Moreover, **Xuan et al.** ⁽¹⁸⁾ have detected significant differences in quality of life of psoriasis patients treated with metformin plus methotrexate, compared to those treated with methotrexate alone.

Regarding the safety of metformin administration in patients with psoriasis and diabetes, it did not cause increased mortality, did not increase the severity of psoriasis or the rate of hospitalization for any other reason ⁽¹⁹⁾.

Wu et al. ⁽²⁰⁾ investigated the risk of developing psoriasis in patients with diabetes depending on the antidiabetic medication. In individuals with severe diabetes treated with insulin, they found an increased risk of psoriasis development, while metformin therapy did not have such effect. One case of psoriasis has been linked to metformin use, however the rash subsided and returned after the medication was discontinued ⁽²¹⁾.

The anti-inflammatory effects of metformin:

Metformin's anti-inflammatory properties have yet to be fully explained. The hallmark of psoriasis, cell proliferation inhibition, may be caused by the activation of AMPK in the extracellular signal-regulated kinase (ERK1/2) signaling pathway, which then inhibits cell proliferation ⁽²²⁾.

The HaCaT cells are keratinocyte-derived cell lines whose excessive proliferation results in psoriatic lesions and, hence, they are commonly used as an in vitro model for the study of anti-psoriasis agents. **Berekméri et al.** ⁽²³⁾ discovered that metformin suppressed cell growth in HaCaT cells by increasing phosphorylation levels of AMPK and ERK1/2 and activating the mitogen-activated protein kinase signaling pathway.

Mammalian target of rapamycin (mTOR) is a molecule in the AMPK pathway that receives signals from growth factors, cytokines, and metabolic circumstances to regulate glucose and lipid metabolism, as well as cell growth, proliferation, and survival ⁽²⁴⁾. Effector T cells are activated via the mTOR pathway, while mTOR-deficient T cells are activated into Treg cells. Pathological circumstances are linked to increased mTOR signaling. Through AMPK activation, metformin has been proven to have a considerable impact on inhibiting mTOR's phosphorylation ⁽²⁵⁾.

T-lymphocyte proliferation and differentiation are regulated by AMPK, but it also has a significant impact on immune cell activity, such as macrophage, neutrophil, and DC activity ⁽²²⁾.

Anti-inflammatory AMPK activators could be developed, and existing ones could be repurposed, because of current information of their anti-inflammatory properties. It has been suggested that the use of metformin, an AMPK activator, could be used to treat several autoimmune and inflammatory illnesses ⁽²⁶⁾.

For methotrexate-treated psoriasis patients, particularly those with metabolic syndrome, metformin

may have an additional anti-inflammatory effect. Metformin, on the other hand, has been shown to reduce methotrexate's hepatotoxicity in animal studies ⁽²⁷⁾.

Pharmacokinetics of metformin:

Specific carrier/transporter systems transport metformin into cells, including intestinal enterocytes. Bioavailability after oral ingestion is influenced by dosage, where greater doses result in less absorption. Metformin is primarily eliminated from the body through the kidneys, thanks to proteins that are involved in drug and toxin extrusion ⁽²⁸⁾.

When it comes to the safety and efficacy of metformin, it has been demonstrated to be both. However, after taking it, you may experience a number of unwanted side effects. An altered or metallic taste in the mouth may also be a symptom of gastroesophageal reflux disease. Other symptoms include nausea and abdominal bloating, flatulence, vomiting, diarrhea, constipation, heartburn, headache, agitation, dizziness, chills, and exhaustion ⁽²⁹⁾. Rare side effects of metformin include hepatitis, skin rash, itching, flushing, and decreased vitamin B12 absorption. Lactic acidosis may rarely develop, necessitating immediate discontinuation of metformin ⁽³⁰⁾.

Furthermore, metformin has several contraindications, including pregnancy, ketoacidosis, liver cell failure, kidney failure, respiratory failure, circulatory failure and severe infection ⁽³¹⁾.

CONCLUSION

Metformin and methotrexate may enhance psoriasis patients' clinical results by improving metabolic syndrome parameters due to their anti-proliferative and anti-inflammatory actions.

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