

REVIEW ARTICLE

Metformin. Its use in dermatology. Small bibliographic review on the subject.

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ABSTRACT

Metformin is currently and for many years, the treatment of choice for millions of patients affected by type 2 diabetes mellitus. Approximately since 2010, several dermatological diseases such as hirsutism, hidrosadenitis suppurativa, acne and other processes are reported to be treated with this drug with promising results but also with undesirable side effects. We will make a small bibliographic review of the subject focusing especially on its dermatological uses.

INTRODUCTION

Metformin is a biguanide well known for being a drug especially used in the treatment of type 2 diabetes mellitus. Historically this product, native to Central and Southern Europe, Asia Minor and Iran, is linked to *Galega officinalis* (Photo No. 1) which is also known as goat's rue, French lilac or teacher's herb, among other names, a medicine of traditional medieval use in the Old World, rich in guanidine and which as early as 1918 was shown to reduce blood glucose; although it was used as early as 1772 to reduce blood glucose, However, since 1772 it was already used to treat the symptoms of diabetes such as polyuria and polydipsia,² to be later forgotten, being in the 1940s when it was rediscovered as a useful drug to treat influenza, noting then that in these patients with influenza, there was a decrease in blood glucose. We can summarize by indicating that this drug (1,1-dimethylbiguanide hydrochloride) has been the most widely used glucose-lowering drug for the last 60 years and is the first-line pharmacological product for patients recently diagnosed with type 2 diabetes mellitus, and it is esti-



Photo No.1. *Galega officinalis*. Taken from Wikipedia

mated that it is currently used daily by more than 200 million patients, either as monotherapy or in combination with sulfonylureas or dipeptidyl 1 peptidase inhibitors.³ The name *Galega* comes from the Greek gala, meaning milk, and ega, meaning to provoke, since it was used as a galactogen in small domestic animals (taken from Wikipedia).⁴

In adults, treatment with metformin is usually started with a dose of 500 mg to 850 mg twice daily, which can be increased by 500 mg every week or 850 mg every two weeks until a maximum dose of 2550 mg is reached.⁵

We should not forget that this drug is not exempt from adverse effects. It is estimated that 10% of these effects include gastrointestinal disturbances, headache, skin rash, dizziness, vitamin B12 deficiency, hypoglycemia, hemolysis and, less frequently and always associated with high doses, lactic acidosis, which can occur together with other complications such as renal failure and hepatic dysfunction, without neglecting the possibility of metformin intoxication.⁶ The possibility of nightmares and abnormal dreams has also been reported with the administration of this drug and attributed to an alteration of cerebral glucose during the night; nocturnal hypoglycemia, although it is usually clinically asymptomatic, can cause discomfort related to poor sleep quality.⁷

Although there are unknowns about the exact mechanism of action of metformin due to its complexity and difficulty in understanding it, it has been possible to determine certain aspects of great importance about its mechanics of action³:

- Liver and intestine are the main target organs of this drug.
- Mitochondria and lysosomes are the target organelles for the hypoglycemic activity of metformin.
- Host-intestinal microbiota interaction contributes to the therapeutic effects of metformin.
- Metformin has anti-inflammatory and immunomodulatory capacity in several pathologies related to the immune system, through AMPK (AMP-activated protein kinase) enzyme-dependent and -independent mechanisms involving both the innate and adaptive immune systems.
- Metformin therapy in patients with type 2 diabetes mellitus enhances the release of the cytokine GDF15, which may facilitate weight loss, but does not necessarily reduce blood glucose levels.

CONTRAINDICATIONS

Regarding contraindications for the use of metformin, two essential points could be indicated, the first one, hyper-

sensitivity to this drug and the second one, patients with high risk of lactic acidosis among which are included³:

1. Moderate renal insufficiency
2. Cases of acute and chronic metabolic acidosis including diabetic ketoacidosis.
3. Cases of hypoxemia such as decompensated heart failure, respiratory failure, etc.
4. Hepatic insufficiency, chronic alcoholism

NEW INDICATIONS FOR METFORMIN: DERMATOLOGY

In recent years, interest has intensified in new uses of this drug that allow addressing the treatment of metabolic syndrome, polycystic ovary syndrome, hyperandrogenic states and lately multiple dermatological pathologies, such as inflammatory skin diseases such as, psoriasis or hidradenitis suppurativa, skin cancer demonstrating antitumor properties, dermatoses related to endocrine pathology, such as hirsutism or acanthosis nigricans and the use of metformin topical cream, which has shown good results in the treatment of melasma.^{5,8,9}

We know that hyperandrogenism associated with hyperinsulinemia and insulin resistance can play a significant role in the appearance of various dermatological processes. Insulin resistance is characterized by decreased cellular glucose uptake. The cytoplasmic fraction of the insulin-sensitive glucose transporter 4 (GLUT4) is significantly decreased and metformin counteracts this process allowing a greater glucose uptake and therefore a decrease in insulin resistance, all of which gives metformin a marked importance in the treatment of different dermatoses.¹⁰

METFORMIN IN ACNE VULGARIS

We know that the pathogenesis of acne vulgaris is associated with a strong increase in androgens, growth hormone and its mediator, insulin-like growth factor 1 (IGF-1). This hyperandrogenism, IGF-1 elevation and insulin resistance are also associated with polycystic ovary syndrome, which has a strong influence on the persistence and severity of acne. Metformin improves insulin sensitivity and inhibits lipogenesis and also decreases IGF-1 bioavailability in patients with polycystic ovary syndrome.

If we consider that moderate to severe acne, despite therapeutic advances, continues to be a dilemma on many occasions and that patients often express concern about antibiotic or isotretinoin treatments, other options are necessary and this gives importance to complementary treatment with metformin.¹¹

The efficacy of metformin in patients who do not have polycystic ovary syndrome is of limited knowledge. There is a study that tells us that metformin can be used as an adjunctive therapy in acne, by inhibiting the mechanics of the rapamycin complex 1 (mTORC1), however, and despite a consensus on the benefits of the use of metformin in acne, studies are still needed to know the mechanism of action of this drug in this pathology.¹²

In a study conducted in patients with acne¹³ it was suggested that the mechanism of action was not entirely attributable to its direct action against insulin resistance. If we think that oral administration of metformin improves glycemia and that IV administration does not achieve the same result, we can deduce that the action of metformin could be related to the intestine. On the other hand, it has long been known that acne vulgaris affects some gastrointestinal mechanisms, and these authors conclude that their work demonstrates that metformin could treat moderate to severe acne by regulating the intestinal microbiota.¹³

Rosas et al. reviewed several articles on the same subject and concluded that metformin produces a notorious improvement in acne, reducing both inflammatory and non-inflammatory lesions with relatively few adverse effects, the most notorious being abdominal distension and distension, as well as headache, all of which are self-limiting.¹⁴

In the study performed by Albalat et al.¹⁵ in 50 patients in which IGF-1 (insulin-like growth factor 1) levels were investigated in all, before and after administration of metformin, based on the fact that in another study performed by Rahaman et al.¹⁶ in patients with acne, elevated serum IGF-1 levels were found and that this level correlated with the severity of acne, being higher among severe cases than among mild and moderate cases. These

patients were treated with metformin and a statistically significant decrease was demonstrated, suggesting that elevated IGF-1 level and insulin resistance play a role in patients with acne and concluding that especially in those cases resistant to other therapies, metformin may play an interesting role in decreasing their severity as well as the count of inflammatory lesions.

METFORMIN IN HIDRADENITIS SUPPURATIVA

This process consists of a chronic cutaneous and systemic inflammation, which involves areas of the skin with apocrine glands located mainly in the axillae, groin and anogenital areas, with inflammatory, painful and deep lesions in the form of nodules, abscesses and fistulas that leave cribriform scars accompanied by contractures and usually begins in the post-pubertal stage. Follicular occlusion, as a consequence of follicular epithelial hyperplasia is very important in the pathogenesis of hidradenitis suppurativa which subsequently leads to cyst formation, inflammation and subsequent follicular rupture. Although the pathogenesis of this process has not yet been clearly established, it has been found to be associated with diabetes, hypertension, hyperlipidemia, metabolic syndrome, insulin resistance and obesity.¹⁷ The authors conclude that metformin is an effective, well-tolerated and inexpensive treatment with the additional advantage of improving insulin resistance, which is a frequent comorbidity.

In another report of a 22-year-old patient with hidradenitis suppurativa, overweight but without insulin resistance or presence of polycystic ovaries, who had received topical and oral antibiotics for months, topical aluminum chloride and intralesional corticosteroids, all with very little response. Given these disappointing results, metformin was administered and surprisingly after 12 days, the lesions remitted and one year later she was still free of lesions. Metformin could be an excellent option for the management of this disease.¹⁸

METFORMIN IN ACANTHOSIS NIGRICANS

This process is characterized by thickening and hyperpigmentation of the skin affecting the axillae, groin,

neck, nape of the neck, submammary region and articular skin on the back of the hands. It is classified according to etiology as benign familial, obesity-associated, syndromic, malignant, drug-induced and mixed. The benign form has been clearly related to obesity, hyperinsulinemia and insulin resistance, the most commonly used treatments being rosiglitazone, octreotide, vitamin D analogs, retinoic acid and metformin, which has been accepted as beneficial for the treatment of this condition, with good results reported even in obese children with this problem, especially when combined with lifestyle changes, which contributes to a decrease in body mass index.^{19,20}

There are reports of successful treatment of very intense acanthosis nigricans, combining systemic therapy to act on the underlying causes and cosmetic topical therapy to achieve faster clinical response. Metformin 850 mg/day was administered to a patient with a severe case, in addition, an oral contraceptive with drospirenone/ethinylestradiol was prescribed to reduce hyperandrogenism and improve polycystic ovary syndrome, hypocaloric diet (150 Kcal) and physical activity to reduce hyperinsulinemia. To the above, tacalcitol QD cream was added, obtaining marked improvement after 2 months of treatment, especially in the neck and armpits.²¹

In summary, treatment is based first of all on resolving the underlying causes. Topical agents are the first choice when the underlying cause is unknown or in the familial form, the most commonly used being keratolytics, lightening agents, topical steroids (useful when combined with other agents), while systemically metformin and rosiglitazone have shown benefits in AN with insulin resistance.²²

METFORMIN IN HIRSUTISM

Hirsutism is a condition in which there is an excessive amount of mature hair in androgen-dependent body areas, which means a percentage of affection in women between 5 and 10% causing an alteration in the quality of life and in their emotional background, since others define it as the abnormal development of male pattern hair on a woman's body. Among its causes, 75 to 80% of the cases are due to polycystic ovary syndrome asso-

ciated to high levels of androgens, between 5 and 20% are idiopathic and less than 5% to infrequent causes such as non-classical congenital suprarenal hyperplasia, androgen-dependent tumors, Cushing's syndrome and reactions to drugs.²³

In various studies such as those of Barrionuevo et al.,²⁴ it was demonstrated that the combination of oral contraceptives and insulinsensitizers or anti-androgenic drugs and insulinsensitizers were associated with a statistically significant reduction in hirsutism, and with regard to specific drugs, the combination of contraceptive pills and metformin or flutamide and metformin obtained similar results, but further studies are needed.²⁴ Other authors claim that reducing circulating levels of insulin reduces the amount of free testosterone in the circulation, suggesting that metformin was useful in the treatment of hirsutism.²⁵

METFORMIN IN PSORIASIS

Psoriasis is a chronic inflammatory disease with genetic, immunological and metabolic etiology. Some studies have shown the benefits of metformin in patients with psoriasis.

We know that in psoriasis there is an increased risk of systemic disorders such as obesity, metabolic syndrome, diabetes mellitus and cardiovascular morbidity and that, in these patients, many inflammatory factors such as TNF alpha, IL-6, IL-8, IL-12, IL-17, IL-19 and IL-23 are overproduced, all of which leads to metabolic syndrome.²⁶

Patients with diabetes have a higher risk of developing psoriasis, which is why it is interesting that these diabetic patients have a lower risk of psoriasis if they use metformin frequently, compared to those who use it occasionally.²⁶

The authors conclude by summarizing that:

- metformin plays an important role in autoimmune diseases,
- better results are obtained by combining methotrexate with metformin compared to methotrexate alone.
- even with topical therapy combined with metformin, results are obtained,

- d) metformin decreases the risk of developing psoriasis in diabetic patients.
- e) good results in patients with psoriasis and metabolic syndrome, with metformin being beneficial in both cases.²⁷

In another study²⁸ of 66 patients in which the combined therapy of metformin plus methotrexate vs. methotrexate alone was evaluated in patients with psoriasis and metabolic syndrome, a much more pronounced improvement was determined in the patients of the first group than in those treated with monotherapy alone, not only in their psoriasis but also in their blood sugar and triglyceride levels approximately three months after starting treatment, with no adverse effects with this combined therapy.

A meta-analysis²⁶ on 148 patients was published this year on the efficacy of metformin in the treatment of psoriasis based especially on the fact that this drug can serve as an anti-inflammatory agent by activating adenosine monophosphate-activated protein kinase in the kinase signaling pathway, which subsequently inhibits dendritic cell and T-cell activation and cell proliferation, all of which increases the efficacy of metformin treatment in psoriasis. This study verified this claim, with both PASI and ESI (erythema, encrustation and induration) reduced by 75% in both cases. The study confirmed a significant improvement of metabolic syndrome parameters with beneficial effect on fasting glycemia, triglycerides, total cholesterol and LDL cholesterol in patients with psoriasis.²⁶

Several studies have mentioned that metformin can be useful in the treatment of psoriasis when combined with methotrexate,²⁹ in both cases they share the same target, the protein kinase pathway that we mentioned above. On the other hand, animal studies affirm that metformin can reduce the hepatotoxicity caused by the use of methotrexate in the long term and the present study was carried out in order to prove the efficiency and safety of this combined therapy in psoriasis.²⁸

Finally, a cohort study was published using the National Health Insurance Research Database to determine the safety of metformin use in psoriasis patients with diabetes mellitus. The results determined that metformin can be prescribed to diabetic patients

with psoriasis without safety concerns.³⁰

METFORMIN IN MALIGNANT SKIN TUMORS

Metformin has been associated with a decreased risk of cancer in patients with type 2 diabetes. Several epidemiological studies suggest that metformin prevents cancer but its effects on skin cancer remain to be known. This work evaluated whether metformin use could be associated with a decreased risk of skin cancer using the National Health Insurance database.³¹ The published results support the protective effect of metformin on skin cancer when used for 4 years and with a cumulative dose of 1,594,000 mg, but of course further studies are needed.

In another study published in 2021 and conducted in Iceland with metformin, based on its anti-aging and anticarcinogenetic effect and using studies of the entire Icelandic population using ICR banks and the Icelandic Prescription Drug Registry, they concluded that metformin is associated with a decreased risk of BCC and should be considered in the future as a chemoprotective agent in patients at increased risk of BCC.³²

Finally, another report on metformin and melanoma indicates that this drug, also acting on the protein kinase pathway, causes a decrease in protein synthesis and cell proliferation. It is known that metformin decreases the risk of cancer compared to other antidiabetic treatments. They conclude by stating that metformin, and biguanides in general, are good prospects for the development of new therapies against melanoma, given their action on metabolism and the activation of cell death mechanisms in melanoma cells.³³

CONCLUSION

All the works point towards new uses of an old drug in dermatological pathology, with the advantage of promising results that in some cases are already realities and with a spectrum of very limited adverse effects that generally do not prevent its use. Acne, acanthosis nigricans, psoriasis, are clear examples of the benefit of this drug as a therapeutic complement and with a very promising horizon of a possible anticancer action within the dermatological oncology panorama.

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