CHAPTER 24

METFORMIN

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Metformin (1,1-dimethylbiguanide), a biguanide derivate, is regarded as an antihyperglycemic agent because it lowers blood glucose concentrations in type 2 diabetes (T2D) without causing overt hypoglycemia.[1]

It is the first line of treatment in overweight and obese T2D patients as it has been shown to improve the clinical outcome and the quality of life in these patients as well as decreasing their microvascular and macrovascular complications.[2]

Metformin has pleiotropic actions on several tissues sensitive to the primary effect of insulin or affected by insulin resistance, such as the liver, the skeletal muscles, the adipose tissue, the endothelium and the ovaries.[3] Metformin is known to reduce hyperinsulinemia and insulin resistance mainly by decreasing liver gluconeogenesis and by improving glucose disposal in muscle. Insulin may bind and activate insulin-like growth factor 1 (IGF-1) receptors (IGF-1Rs), which have a more potent mitogenic and transforming activity than insulin receptors. Metformin could block the mitogenic effects of insulin and IGF-1 at the post-receptor level; however, the traditionally accepted mechanism is not direct (*via* post-receptor actions), but rather indirect, through an insulin-sparing effect.[4]

Recent clinical trials suggest that metformin, in addition to its efficacy in treating T2D, may also have therapeutic potential in other conditions including diabetic nephropathy, cardiovascular diseases, polycystic ovary disease (PCOS) and the prevention or treatment of cancer.[1] On the other hand cutaneous conditions and cutaneous side-effects have also associated with merformin use.

ACANTHOSIS NIGRICANS

Acanthosis nigricans (AN) appears as hyperchromic plaques, with vegetative, lichenified or papillomatous surfaces, dark brown to black coloration, located in the armpits, groin, neck and other intertriginous areas[5], histopathologically characterized by papillomatosis and hyperkeratosis of the skin.[6] More recently, it has been divided into 8 subtypes: benign, obesity-related, syndromic, malignant, acral, unilateral, secondary to medication and multifactorial. This dermatosis is often related to endocrine disorders, such as obesity, insulin resistance (IR), T2D and PCOS. Due to the rising prevalence of obesity and diabetes a high prevalence of AN has been observed recently.

Therapeutic approach involves treatment of underlying disease or tumor, cessation/avoidance of the inciting agent in drug-induced AN, use of topical/oral agents and cosmetic surgery.[6]

There are reports of the use of oral and topical retinoids with good results. In addition, other keratolytic agents can be used. Oral treatments include isotretinoin and metformin. Procedures include dermabrasion and Alexandrite laser, described more recently.[5]

Insulin has been demonstrated to cross dermoepidermal junction to reach keratinocytes. At low concentrations, insulin regulates carbohydrate, lipid and protein metabolism and can weakly promote growth by binding to "classic" insulin receptors. At higher concentrations, however, insulin can exert more potent growth-promoting effects through binding to IGF-1Rs that are similar in size and subunit structure to insulin receptors, but bind IGF-1 with 100- to 1000-fold greater affinity than insulin. The binding stimulates proliferation of keratinocytes and fibroblasts, leading to AN[6]. Therefore, metformin is useful in AN characterized by IR. Metformin reduces glucose production by increasing peripheral insulin responsiveness, reduces hyperinsulinemia, body weight and fat mass and improves insulin sensitivity.[6]

ACNE VULGARIS

Acne vulgaris is an inflammatory pilosebaceous disease characterised by comedones; papules; pustules; inflamed nodules; superficial pus-filled cysts; and (in extreme cases) canalising and deep, inflamed, sometimes purulent sacs[7]. The pathogenesis of acne is multifactorial and includes abnormal follicular keratinization, increased production of sebum secondary to hyperandrogenism, proliferation of Propionibacterium acnes and inflammation.[8] Acne is the most common skin disease of adolescence, affecting over 80% of teenagers (aged13-18 years) at some point.[7] Acne vulgaris has a substantial impact on a patient's quality of life, affecting both self-esteem and psychosocial development.[8]

duced, the woman presented with the similar general cutaneous eruption.[31]

Metformin-induced leukocytoclastic vasculitis was reported in a 60-year-old woman. The temporal relationship between metformin administration and the occurrence of vasculitis, with clinical improvement observed following drug discontinuation.[30]

Kastalli et al. was reported 3 cases of photosensitivity induced by metformin. Lesions healed after stopping metformin in all cases with positive rechallenge in the one case.[32]

In previously study, Mumoli et al. was reported for the first time a non vasculitis facial skin manifestation related to metformin in a young woman, rosacea-like facial rash.[33]

Although metformin may be considered to be effective in the treatment of psoriasis, psoriasiform drug eruption due to use of metformin has been reported. Koca et al. was reported a case of a psoriasiform eruption associated with metformin use, which cleared after withdrawal of the drug and reappeared on rechallenge.[34]

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