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An Overview of Research on the Use of Oral Hypoglycaemic to Treat Acanthosis Nigricans

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ABSTARCT:
The dermatological condition known as Acanthosis Nigricans (AN) is typified by thicker, velvety, hyperpigmented plaques that are primarily found in intertriginous areas like the neck, axillae, and groyne. Insulin resistance, the underlying condition of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM), is frequently linked to AN. Hyperinsulinemia, which promotes keratinocyte and fibroblast proliferation through insulin-like growth factor-1 (IGF-1) receptor pathways, is a pathophysiological component in AN.Oral hypoglycaemic medications, which are mostly used to treat type 2 diabetes, have been investigated for their possible therapeutic benefits in AN because to the strong correlation between AN and insulin resistance. The purpose of this review is to investigate the clinical consequences, mechanisms, and effectiveness of treating AN with metformin and other oral hypoglycaemics.By stimulating AMP-activated protein kinase (AMPK), decreasing hepatic gluconeogenesis, and increasing peripheral glucose absorption, biguanide metformin has shown considerable effectiveness in improving insulin sensitivity and lowering circulating insulin levels. Metformin is able to successfully lessen the severity of AN lesions in individuals with insulin resistance or type 2 diabetes, according to clinical evidence from research and case reports. Though their usage is constrained by side effects and a lack of comprehensive clinical data, other oral hypoglycaemics, such as glucagon-like peptide-1 (GLP-1) agonists and thiazolidinediones (TZDs), have also demonstrated potential benefits in treating AN.In addition to highlighting the need for more research to establish standardized treatment procedures and assess long-term efficacy and safety, this review also highlights the potential of oral hypoglycaemics as a therapy option for AN. The results highlight the significance of treating insulin resistance in the treatment of AN and imply that oral hypoglycaemics, especially metformin, may be a useful addition to the toolkit for treating this illness.

KEYWORDS:Acanthosis Nigricans, Insulin Resistance, Oral Hypoglycaemics, Metformin, Type 2 Diabetes Mellitus

I. INTRODUCTION:

The first description of Acanthosis nigricans (AN) was made in Germany in 1889 by Unna and Pollitzer. By 1909, there were about 50 cases of AN reported, and internal tumors were taken into consideration. Kahn et al. carried out the first study to explain the connection between AN and insulin resistance, which was published in 1976. The American Diabetes Association officially identified AN as a risk factor for the onset of diabetes in children in 2000[1].Skin conditions like ANcan show up as thick, velvety, dark patches in the groin, armpits, and neck. Insulin resistance, a defining feature of diseases like obesity, metabolic syndrome, and type 2 diabetes mellitus is commonly associated with AN. The distinctive skin alterations in these circumstances are partly caused by elevated insulin levels, which drive keratinocyte and fibroblast proliferation via the insulin-like growth factor receptor[2].Hyperinsulinemia plays a role in the pathophysiology of AN by stimulating the proliferation of keratinocytes and dermal fibroblasts by activating insulin-like growth factor-1 (IGF-1) receptors, which results in recognizable skin alterations. Even while dietary and activity changes are essential for controlling insulin resistance, pharmaceutical treatments—especially oral hypoglycemics—have been investigated for their ability to treat anaemia of gravity[3].Even while dietary and activity changes are essential for controlling insulin resistance, pharmaceutical treatments—especially oral hypoglycemics—have been investigated for their ability to treat anemia of gravity. The biguanide metformin has demonstrated notable effectiveness in enhancing insulin sensitivity, decreasing hepatic gluconeogenesis,

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and lowering circulating insulin levels, all of which help to alleviate the AN's dermatological symptoms[4-5].While glucagon-like peptide-1 (GLP-1) agonists and thiazolidinediones (TZDs) are two other oral hypoglycemics that show promise, their usage is frequently restricted due to side effects and a lack of comprehensive clinical evidence. To better understand how these oral hypoglycemics work to treat anemia, this review will look closely at their mechanisms, effectiveness, and clinical consequences[6].

PATHOPHYSIOLOGY :

The complicated skin condition known as acanthosis nigricans (AN) is caused by multiple interconnected pathophysiological pathways. The development of this condition is closely linked to insulin resistance; however, genetics and hormonal effects are also important determinants. This is a thorough analysis of the pathophysiology of AN[7]:

Hyperinsulinemia and Insulin Resistance:

Central Mechanism:

Insulin resistance and the ensuing hyperinsulinemia are the most well-known pathways in the development of AN. The body produces more insulin in insulin-resistant conditions like obesity, metabolic syndrome, and type 2 diabetes mellitus to make up for the decreased effectiveness of the hormone[8]. Through several mechanisms, elevated insulin levels activate dermal fibroblasts and keratinocytes.

- Insulin and IGF-1 Receptors: Insulin-like growth factor-1 (IGF-1) receptors, mainly on keratinocytes and fibroblasts, can bind to and be activated by high levels of circulating insulin. The hyperplasia and papillomatosis that characterize AN are caused by this stimulation, which also suppresses apoptosis and encourages cellular growth[9].
- PI3K/AKT Pathway: The PI3K/AKT signaling pathway is essential for cell growth and proliferation and is downstreamly activated by insulin and IGF-1 receptor activation. This pathway also plays a role in the hyperpigmentation and thickness of AN lesions[10].

Genetic elements :

The pathophysiology of AN is significantly influenced by genetics as well. Mutations in genes related to cell development and differentiation, such as fibroblast growth factor receptor (FGFR), have been connected to familial forms of anemia[11]. Particular syndromes linked to AN comprise:

- Mutations in the FGFR2 gene cause Crouzon Syndrome, a genetic condition marked by anomalies of the craniofacial structure. This disorder can also result in AN[12].
- SADDAN Syndrome: Serious skeletal deformities and ankyloglossia are caused by mutations in the FGFR3 gene[12].

Inflammatory Cytokines and Obesity:

One prevalent comorbidity in people with AN is obesity, which aggravates insulin resistance and raises the risk of hyperinsulinemia. Pro-inflammatory cytokines like TNF-α and IL-6 are secreted by adipose tissue, especially visceral fat, and they hinder insulin signaling and increase insulin resistance[13]. Additionally, these cytokines can directly impact skin cells, which aids in the pathogenesis of AN.

Factors Related to Hormones:

An additional factor in AN can be specific hormonal abnormalities. For example, AN is frequently linked to disorders like polycystic ovarian syndrome (PCOS), which raise androgen levels. Androgens can directly promote keratinocyte growth and aggravate insulin resistance. Furthermore, growth hormones and corticosteroids can influence the insulin and IGF-1 pathways, which can lead to the development of AN when they are overexpressed [14-15].

Acanthosis Induced by Drugs Nigricans:

Several drugs can cause AN by either directly promoting keratinocyte proliferation or raising insulin resistance[16]. Among them are:

- Nicotinic Acid: Nicotinic acid can cause insulin resistance and is used to treat hyperlipidemia[17].
- Hyperinsulinemia and insulin resistance can be made worse by insulin and systemic corticosteroids[17].
- Hormone Therapy: By affecting insulin sensitivity and cellular proliferation, high dosages of estrogen or other hormones may play a role in the development of AN.

THE ACANTHOSIS NIGRICANS EPIDEMIOLOGY:

The disorder known as acanthosis nigricans (AN) has a wide range of prevalence, which is greatly impacted by demographic characteristics like age, race, and underlying

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medical conditions. Those who have insulin resistance, such as those who are obese, have metabolic syndrome, or have type 2 diabetes, are more likely to experience it (T2DM). According to epidemiological research, AN is more common among groups with greater obesity and type 2 diabetes rates[18-19].For example, AN is commonly seen in Native American, African American, and Hispanic communities in the United States, all of whom have higher rates of obesity and insulin resistance. There is a substantial association between obesity and AN, as evidenced by the 50% to 70% prevalence of AN among obese children and adolescents[20]. Studies have indicated that up to 74% of adults with T2DM have AN, underscoring its significance as a dermatological indication of metabolic dysregulation. This link is also seen in adult populations.The prevalence of AN is also influenced by gender, with females being more affected than males[21]. This difference may be attributed to hormonal factors as well as the higher occurrence of disorders such as polycystic ovarian syndrome (PCOS) in women, which is closely linked to both AN and insulin resistance. Age is also a significant role; although AN can strike at any age, it is more commonly diagnosed in young people and during puberty, which coincides with periods of increasing insulin resistance[22].Not only is AN more prevalent in people with metabolic problems, but it is also seen in patients with specific genetic abnormalities and cancers, but these instances are not common. Because AN is caused by mutations in the genes that control fibroblast growth factor receptors, syndromes like Crouzon and SADDAN are linked to AN (FGFR)[23-24]. Compared to benign variants, malignant AN typically affects older persons and manifests with more widespread and quickly growing lesions. It is frequently associated with gastrointestinal adenocarcinomas.All things considered, AN's epidemiology shows a strong correlation with metabolic illnesses, especially those involving insulin resistance. Its existence acts as a significant clinical signal, triggering additional research into possible systemic underlying diseases. Clinicians can identify at-risk people and initiate early therapies to control related metabolic and endocrine diseases by recognizing the epidemiological trends of AN[25].

DERMATOLOGICAL DETAILS:

Dermatologically speaking, acanthosis nigricans (AN) is characterized by hyperpigmented, velvety, thicker plaques that are primarily found in intertriginous areas including the neck, axillae, groin, and occasionally the elbows, knees, and knuckles. The cause of the affected skin's velvety feel, rough appearance, and histologically documented hyperkeratosis and papillomatosis is hyperkeratosis. The lesions are usually scattered symmetrically, and the coloring can range from light brown to black. Though the thicker skin can occasionally produce pruritus or discomfort, AN is mostly asymptomatic[26]. Lesions can get larger and darker in more extreme cases, particularly in people who have malignancies or severe insulin resistance as underlying conditions.Apart from its aesthetic significance, the ailment functions as a clinical indicator for systemic ailments, mainly insulin resistance and related metabolic illnesses like obesity and type 2 diabetic mellitus (T2DM). Significant insulin resistance is indicated by the presence of AN in patients with obesity or type 2 diabetes. Linear accentuations and conspicuous skin marks are seen upon dermatoscopy examination of AN. For clinicians, identifying AN is critical because it triggers the search for underlying metabolic or endocrine abnormalities, which are frequently missed until the skin changes become noticeable[27].

CURRENT MANAGEMENT STRATEGIES OF ACANTHOSIS NIGRICANS:

AN is characterized by thicker, velvety, hyperpigmented plaques that are primarily found in intertriginous areas. Addressing the underlying causes of AN, especially insulin resistance, and utilizing a variety of treatment modalities to enhance the appearance and texture of the skin are essential components of the effective management of AN. The detailed management plans for AN are described below[28].

1. **Treating Lifestyle Changes That Underlie Insulin Resistance**:

The cornerstone of treating AN is increasing insulin sensitivity by lifestyle modifications, especially in those with obesity or type 2 diabetes mellitus (T2DM). Combining food and exercise to lose weight is a very efficient way to lower insulin resistance and, in turn, lessen the severity of AN lesions[29]. Reduced calorie intake, an emphasis on a balanced diet full of whole grains, lean proteins, and vegetables, and a restriction on high-glycemic items that worsen hyperinsulinemia should be the main goals of dietary adjustments. Frequent exercise improves insulin sensitivity and

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aids in weight loss. This includes both aerobic and resistance training[30].

Pharmacological Interventions: Drugs that increase insulin sensitivity are used when lifestyle changes are insufficient. The most often used oral hypoglycaemic medication for this purpose is the biguanide metformin. Metformin lowers insulin levels via increasing peripheral glucose absorption and decreasing hepatic glucose synthesis. Metformin significantly improves the emergence of AN lesions in patients with insulin resistance, according to clinical research[31].

Insulin sensitivity is also increased by other oral hypoglycaemic medications, including as thiazolidinediones (pioglitazone and rosiglitazone), which function as PPAR-γ (peroxisome proliferator-activated receptor) agonists. However, adverse effects like weight gain, edema, and elevated cardiovascular risk frequently prevent them from being used. Although there is little research on their effectiveness, glucagon-like peptide-1 (GLP-1) receptor agonists, which increase glucose-dependent insulin production and encourage weight loss, have showed promise in the treatment of AN[32].

1. Topical intervention:

Although topical treatments are typically less successful than systemic medicines, they are utilized to directly address the hyperkeratosis and pigmentation associated with AN[33].

Keratolytic Agents: Topical keratolytic that help thin out hyperkeratotic skin include urea, salicylic acid, and alpha-hydroxy acids (like lactic acid). These substances function by dissolving keratin, which smoothes the texture of the skin.

Retinoids: Adapalene, tazarotene, and tretinoin are examples of topical retinoids that can help normalize keratinization and improve the appearance of AN. Although they should be introduced gradually and may cause irritation, they encourage cell turnover and minimize hyperkeratosis[34].

Depigmenting Agents: Hyperpigmented lesions can be lightened using topical depigmenting agents like hydroquinone. Tyrosinase is an enzyme that produces melanin; hydroquinone inhibits it, which lessens pigmentation. Azelaic acid and kojic acid are two more substances that have comparable depigmenting properties.

Combination Therapies: To improve efficacy, combination formulations containing keratolytic, retinoids, and depigmenting agents may be used. For example, creams with a triple combination of hydroquinone, corticosteroid, and retinoid can effectively treat certain elements of AN[35].

2. Procedure-Based Care:

Procedure-based therapy might be taken into consideration for patients with severe or resistant AN[36-38].

Laser Therapy: Using lasers to treat AN lesions, such as fractional CO2 laser and long-pulsed alexandrite laser, has shown effective in lowering their thickness and pigmentation. Melanin is the target of these treatments, whereas collagen remodelling is encouraged. However, laser therapy's availability and expense may prevent it from being widely used.

Microdermabrasion: This non-invasive technique can help enhance the look and texture of AN by exfoliating the skin's outermost layer. For patients who are unable to tolerate topical therapies, it is especially helpful.

Chemical Peels: Trichloroacetic acid (TCA) and glycolic acid are two agents that can be used in chemical peels to help lessen pigmentation and hyperkeratosis. These peels encourage the epidermis to lose its outer layers and encourage the creation of new skin.

3. Handling Indirect Causes:

Endocrine Disorders: Treating the underlying illness is crucial when AN is caused by an endocrine disorder, such as Cushing's syndrome or polycystic ovary syndrome (PCOS). An improvement in AN may result from the use of hormonal treatments or surgical techniques to treatthese disorders [39].

Malignancy-Associated AN: It is important to manage the initial malignancy when AN is linked to malignancies, especially gastrointestinal adenocarcinomas, in rare cases. Treatment for the underlying malignancy is frequently followed by the resolution of AN[40].

4. Patient Instruction and Aftercare:

Long-term success depends on teaching patients the significance of controlling underlying diseases, following recommended therapies, and making lifestyle modifications. Comprehensive therapy for AN requires regular follow-up consultations to assess side effects, modify treatment, and track improvement [41].

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USING ORAL HYPOGLYCEMICS TO TREAT AN:

METFORMIN:

Metformin Mechanism of Action: By inhibiting hepatic gluconeogenesis, increasing peripheral glucose absorption, and activating AMP-activated protein kinase (AMPK), the biguanide metformin improves insulin sensitivity[42].

Clinical Support: Metformin therapy has been shown to ameliorate AN lesions in a number of studies and case reports, especially in individuals who also have T2DM or insulin resistance.

Metformin's capacity to reduce insulin levels and enhance systemic insulin sensitivity is primarily responsible for its effectiveness in AN.

Administration & Dosage: To reduce gastrointestinal side effects, metformin is often started at a low dose (500 mg once daily) and gradually titrated to an effective dose (generally 1500-2000 mg/day).

Consequences: gastrointestinal disruptions (diarrhea, nausea) are frequent side effects that are frequently fleeting and dose-dependent. Lactic acidosis is an uncommon yet dangerous side effect.

THIAZOLIDIONES:

Thiazolidinediones (TZDs): PPAR-γ (peroxisome proliferator-activated receptor-gamma) is activated by TZDs like pioglitazone and rosiglitazone, which increase insulin sensitivity by increasing glucose absorption in muscle and adipose tissue[43].

Clinical Support: Due to their insulin-sensitizing properties, TZDs may be beneficial for AN, according to limited research. However, because of side effects like weight gain, oedema, and possible cardiovascular concerns, their use is frequently limited.

Dosage and Administration: The recommended daily dose of pioglitazone is between 15 and 45 mg.

Side effects include increased risk of heart failure, weight gain, fluid retention, and bone fractures.

Glucagon-Like Peptide-1 (GLP-1) Agonists:

Mechanism of Action: GLP-1 agonists inhibit the release of glucagon, decrease stomach emptying, and increase glucose-dependent insulin production.

Clinical Support: Recent research indicates that GLP-1 agonists, like as liraglutide, may lessen insulin resistance and help people lose weight, which could help with AN.

Dosage and Administration: Liraglutide is injected under the skin at a rate of 0.6 mg per day, with dose increases to 1.2–1.8 mg per day contingent upon response and tolerance.

Consequences: GLP-1 agonists can cause nausea, vomiting, pancreatitis, and an increased risk of thyroid cancers [44].

II. CONCLUSION:

Acanthosis nigricans (AN) is a multifactorial dermatological manifestation that is mainly linked to insulin resistance; however, it can also have endocrine, genetic, or paraneoplastic causes. The pathogenesis of the illness is complex, but one important mechanism is hyperinsulinemia, which increases the proliferation of keratinocytes and fibroblasts by binding to insulin-like growth factor-1 (IGF-1) receptors. An important epidemiological pattern is that underlying metabolic conditions like obesity and type 2 diabetes mellitus (T2DM), which are common among some ethnic groups like Native American, African American, and Hispanic populations, are often the cause of this hyperinsulinemia. Hyperpigmented, velvety plaques, found mostly in intertriginous areas, are the clinical manifestation of AN. These plaques are a cutaneous indication of systemic insulin resistance and require a comprehensive evaluation for related metabolic and endocrine diseases. Comprehensive and multidimensional management techniques are employed for AN, with a focus on addressing underlying insulin resistance through lifestyle modifications including exercise and food. These modifications are essential to improve insulin sensitivity and attain weight loss. The use of metformin in particular is a crucial component of pharmacological therapies that reduce hyperinsulinemia and improve AN lesions. The therapeutic benefits of other oral hypoglycaemic medications, such as thiazolidinediones and GLP-1 agonists, are restricted due to their adverse impact profiles. Although they are typically used as an adjuvant to systemic therapy, topical treatments such as retinoids, depigmenting agents, and keratolytics are used to directly improve the appearance of the skin. Procedural procedures, which include chemical peels, laser therapy, and microdermabrasion, offer refractory cases additional alternatives and improve the effectiveness of systemic and topical treatments. Targeted therapy of the underlying illness is necessary for the management of AN resulting from endocrine disorders or malignancies, underscoring the significance of a multidisciplinary approach in these situations. To achieve long-term

success and ensure adherence to treatment regimens, patient education and routine follow-up are essential. In the end, managing AN necessitates a customized, patient-centred strategy that incorporates medication, topical therapy, lifestyle changes, and procedural procedures, all of which are adjusted based on the severity of the illness and its underlying cause. Clinicians can greatly improve the systemic and dermatological outcomes for patients with AN by addressing the underlying reasons and implementing a comprehensive therapy strategy. This highlights the significance of AN as a useful clinical marker for more general metabolic health problems.This all-encompassing approach not only reduces the symptoms related to dermatology but also improves the patient's general health and well-being, which highlights the need for early detection and treatment in cases of AN.

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