

## Review

# The underlying pathogenesis of obesity-associated acanthosis nigricans: a literature review

Evan Eggiman<sup>1</sup> · Steven R. Feldman<sup>2</sup>

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## Abstract

**Background** Acanthosis nigricans (AN) presents as hyperpigmented plaques with ill-defined borders, commonly in intertriginous areas and flexures, and is associated with various factors, including obesity, insulin resistance, and malignancies. Recognizing the clinical significance of ANs relationship with metabolic syndrome and cardiovascular risk is important for early intervention and prevention.

**Purpose** This study describes the metabolic pathways underlying AN, highlighting its association with hyperinsulinemia, insulin-like growth factor 1 (IGF1), leptin, and their receptors. The pathophysiology involves disruptions in insulin, IGF1, leptin, fibroblast growth factor receptors (FGFR) and epidermal growth factor receptors (EGFR), leading to keratinocyte and fibroblast proliferation.

**Methods** A comprehensive literature search through PubMed was performed. Terms such as “Acanthosis nigricans”, “hyperinsulinemia”, “cardiovascular disease”, “diabetes”, “coronary artery disease”, “hyperleptinemia”, “obesity”, “leptin”, “epidermal growth factor”, “insulin resistance”, were brought into consideration. Further articles were found using source materials from included references. Articles published from 1980 to 2023 were used to encompass the broad range of research covered on the subjects.

**Results** AN is connected to insulin, IGF1, leptin, and growth factor receptors and is an independent marker for metabolic disorders.

**Discussion** Dermatologists may intervene by referring to primary care or by addressing underlying causes such as obesity and hyperinsulinemia, emphasizing the importance of weight loss. Various treatments—including medication, topical therapies, and laser modalities—may provide limited improvement. Recognizing AN's significance in cardiovascular and metabolic disease could ote detection and prevention of cardiovascular diseases, improving patient outcomes.

## Key points

AN is an independent marker for metabolic disorders and its potential for further prompting into a metabolic and cardiovascular risk assessments or referral. Recognizing the metabolic connections in AN is important for dermatologists in intervening early and preventing cardiovascular and metabolic comorbidities.

**Keywords** Acanthosis nigricans · Cardiovascular disease · Coronary artery disease · Insulin resistance · Obesity · Leptin · Hyperinsulinemia · Metabolic syndrome · Diabetes

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✉ Evan Eggiman, [e\\_eggiman0716@email.campbell.edu](mailto:e_eggiman0716@email.campbell.edu); Steven R. Feldman, [sfeldman@wakehealth.edu](mailto:sfeldman@wakehealth.edu) | <sup>1</sup>Campbell University School of Medicine, Leon Levine Hall of Medical Sciences, 4350 US Hwy 421 S, 21 Collins Dr. Apt. E, Lillington, NC 27546, USA. <sup>2</sup>Wake Forest University School of Medicine, 4618 Country Club Road, Winston-Salem, NC 27104, USA.



## 1 Introduction

Acanthosis nigricans (AN) is characterized by thickened velvety hyperpigmented plaques. The plaques mainly appear in intertriginous areas and flexures, most commonly on the axilla, neck, and groin, but AN can present on various areas of the body, especially if associated with malignancy. AN can be seen on the elbows, the dorsal joint surfaces of the hands, face, eyelids, genitals, and the oral mucosa [1]. The disease was first described in 1890 in the International Atlas of Rare Skin Diseases and was associated with malignancy. Since that time AN has been linked to endocrinopathies and medication, but most importantly to obesity and insulin resistance.

Obesity is strongly associated with AN [2]. In adolescents, AN prevalence reaches 66% among those above 200% of their ideal body weight, with higher rates in Hispanic (5.5%) and African American (13.3%) individuals [3]. Among obese participants, AN prevalence can be over 60% [4] and as high as 74% of adults attending obesity clinics [5].

AN and metabolic syndrome are associated with hyperinsulinemia. Fasting insulin levels are approximately twofold higher than normal in individuals with AN [6]. In Native American children, AN is an independent marker for insulin resistance, with a prevalence of 73.3% among those with type 2 diabetes [7, 8]. Furthermore, obese students with AN exhibit a markedly higher prevalence of hyperinsulinemia (46.2%) compared to those without either condition (1.4%) [9]. The presence of AN in children is closely associated with glucose intolerance, including impaired glucose tolerance and type 2 diabetes, with fasting plasma insulin concentrations exhibiting the strongest correlation [10]. Among adults aged 35–64 years, the overall prevalence of AN is 16.4%, escalating to 27.2 and 28.2% in males and females with metabolic syndrome [11].

This study aims to describe metabolic pathways underlying the development of AN and their clinical implications. While malignancies (such as gastric adenocarcinoma) can cause AN, this review focuses on the more common cause of AN, obesity, providing information on the relationships with insulin resistance, leptin and metabolic disorders and the potential for dermatologists to intervene to prevent cardiovascular comorbidity.

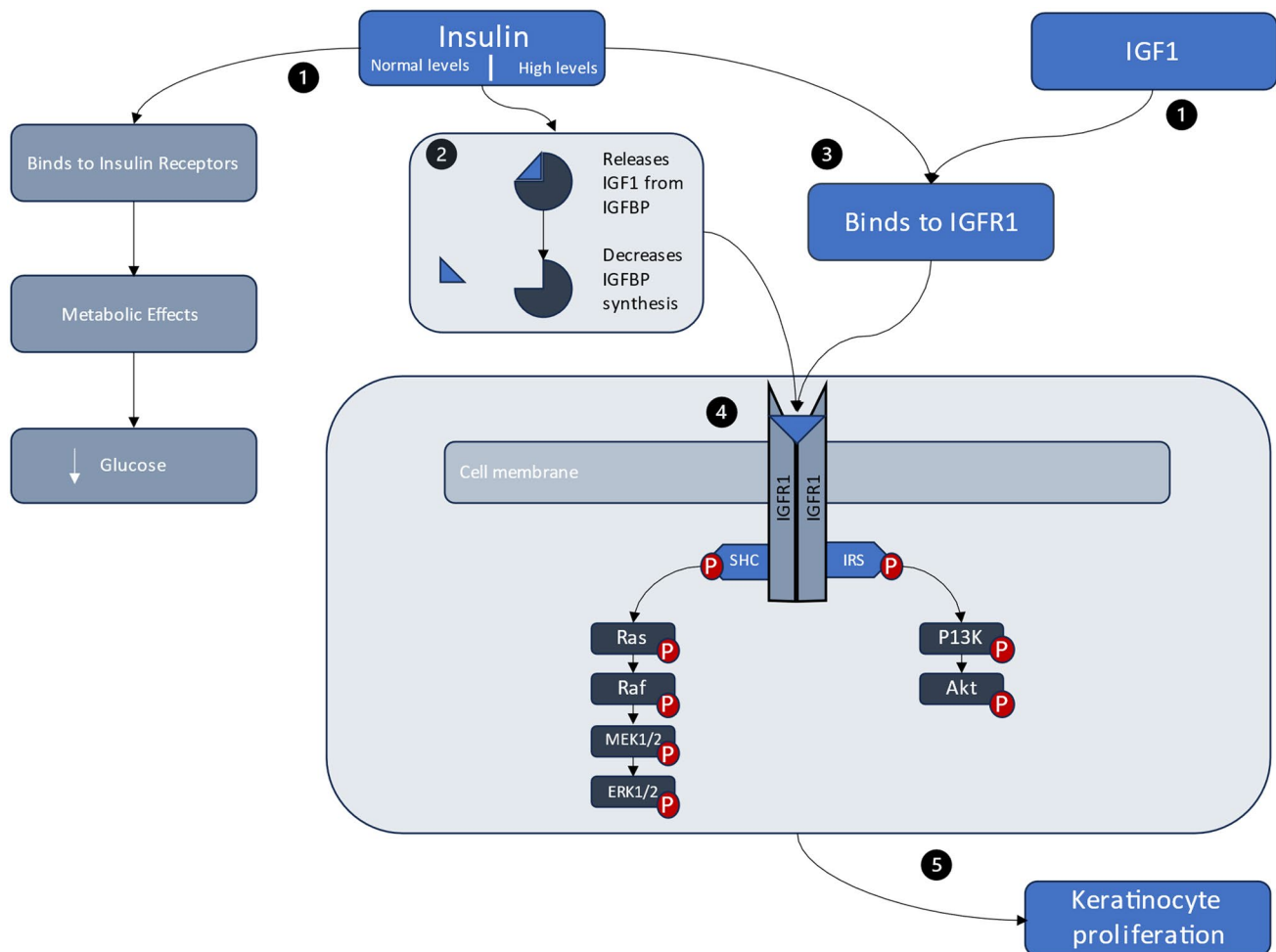
## 2 Pathophysiology

### 2.1 Role of insulin and insulin receptors

The development of AN is associated with obesity and diabetes mellitus, suggesting a potential role for hyperinsulinemia in the pathogenesis of the skin condition. AN mediators include insulin and its receptors, as well as insulin-like growth factor 1 (IGF1) and its receptors. IGF1, a hormone structurally similar to insulin, is primarily produced in the liver in response to growth hormone but can also be synthesized in other tissues, including fibroblasts in the skin [12, 13]. In normal physiological conditions, insulin binds with high affinity to the insulin receptor, exerting metabolic effects, while IGF1 binds with the highest affinity to the IGF1 receptor (IGF1R), promoting mitogenic effects [13]. However, in metabolically unhealthy individuals, elevated insulin levels can disrupt the balance and directly stimulate IGF1R on keratinocytes and dermal fibroblasts, strongly activating the Ras/MAP/ERK and PI3-K/Akt kinase cascades and promoting cell proliferation, resulting in acanthosis, hyperkeratosis, and papillomatosis [12, 13]. Furthermore, high levels of insulin can not only directly stimulate IGF1 receptors but also reduce the synthesis of IGF binding proteins and displace IGF1 from its binding proteins, further enhancing IGF receptor activation [12, 14–16]. This direct stimulation of IGF1R and increased levels of IGF1 lead to fibroblast and keratinocyte proliferation, ultimately contributing to the development of AN (Fig. 1). AN developing at repeated insulin injection sites and in insulin-resistant syndromes further support this mechanism [17–20].

### 2.2 Role of growth factor receptors

Another mechanism of AN involves the activation of fibroblast growth factor receptors (FGFR) and epidermal growth factor receptors (EGFR). FGFR, EGFR, and IGF1 are members of the same tyrosine kinase family and share similar downstream effects [12]. Certain malignancies, particularly gastric adenocarcinoma, may induce AN through a paraneoplastic phenomenon by stimulating these receptors. These malignancies result in increased levels of transforming growth factor alpha (TGF- $\alpha$ ), which binds to EGFRs and promotes epidermal proliferation [15, 20–22]. Hereditary disorders have also been linked to AN as mutations in FGFR genes also contribute to this pathway. TGF- $\alpha$ , a mitogenic polypeptide belonging to the epidermal growth factor family, activates the classical MAPK/ERK pathway, the PI3-K/Akt kinase pathway,



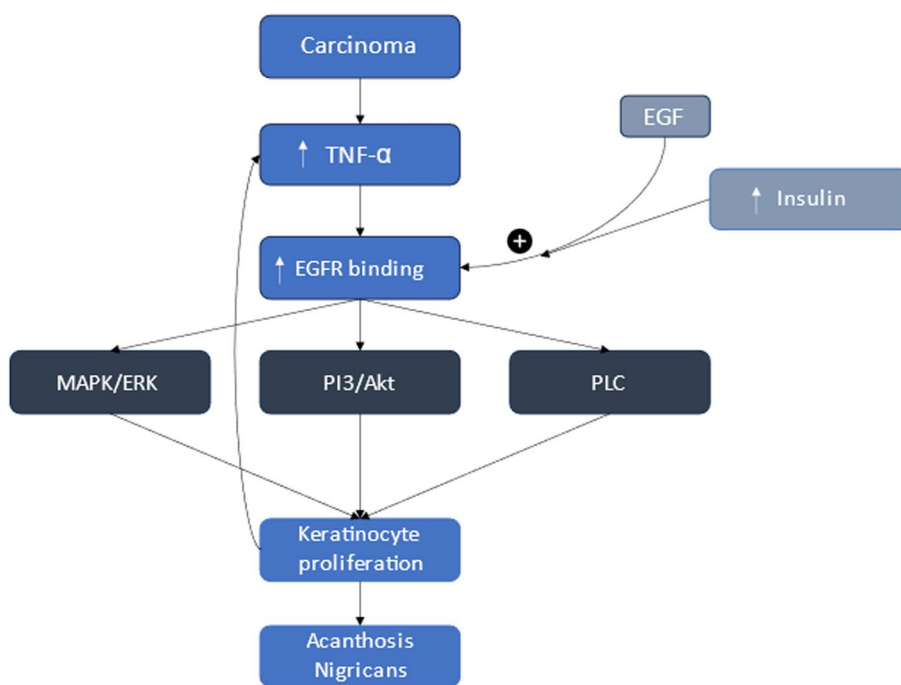
**Fig. 1** Acanthosis Nigricans and the insulin pathway. 1. At normal physiological levels insulin has high affinity for insulin receptors and induces metabolic effects. IGF1 has high affinity for IGF1R and has mitogenic effects. 2. At high levels insulin directly binds to IGF1R to cause mitogenic effects. 3. At high levels insulin decreases IGF1R synthesis and displaces IGF1 from IGF1R equally higher amounts of free IGF1 that can bind to IGF1R. 4. Once insulin or IGF1 binds to IGF1R it activates the Ras/MEK/ERK pathway and the P13k/Akt pathway. 5. This results in keratinocyte proliferation and Acanthosis Nigricans

and phospholipase (PL) C- $\gamma$  pathways when it binds to EGFR, leading to keratinocyte proliferation, differentiation, and migration [15, 21]. Binding of EGFR on keratinocytes can also trigger the production of self-ligands, including TNF- $\alpha$ , creating a feedforward autocrine cycle (Fig. 2). This mechanism may be interconnected with hyperinsulinemia, as high levels of insulin or IGF1 increase the binding of epidermal growth factor (EGF) to EGFR on keratinocytes, and evidence suggests cross talk between EGFR and IGF1R [23, 24]. These findings support the exploration of hyperinsulinemia as a potential contributor to the pathogenesis of AN.

### 2.3 Role of leptin

Leptin is also involved in skin proliferation and obesity-related skin disorders. Leptin, encoded by the Obese (Ob) gene, is a protein hormone primarily secreted by adipose cells, with its production directly proportional to the number of adipocytes in the body [25–27]. While its most well-known function is appetite suppression and energy homeostasis, leptin has other effects. Under normal physiological conditions, leptin circulates through the bloodstream and crosses the blood–brain barrier to bind to leptin receptors in the hypothalamus [25–28]. Binding of leptin to the long form of its receptor (LepRb or ObRb) in the hypothalamus activates the tyrosine protein kinase JAK2 [28, 29]. This activation leads to the phosphorylation of tyrosine and activation of the MAPK, STAT5, and STAT3 pathways resulting in the regulation of food intake and energy homeostasis [25, 28].

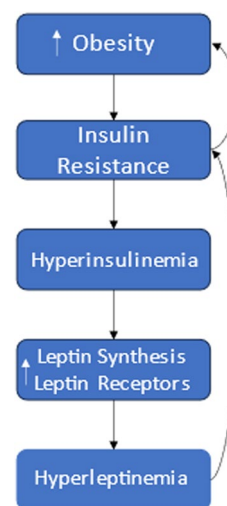
**Fig. 2** Acanthosis Nigricans and the TNF- $\alpha$  pathway. Tumor cells secrete TNF- $\alpha$  resulting in increased serum levels. TNF- $\alpha$  binds to EGFR and activates the MAPK/ERK, P13/Akt, and PLC pathways, which leads to keratinocyte proliferation and AN. High insulin levels increase the binding of EGF on EGFR resulting in more activation and more keratinocyte proliferation

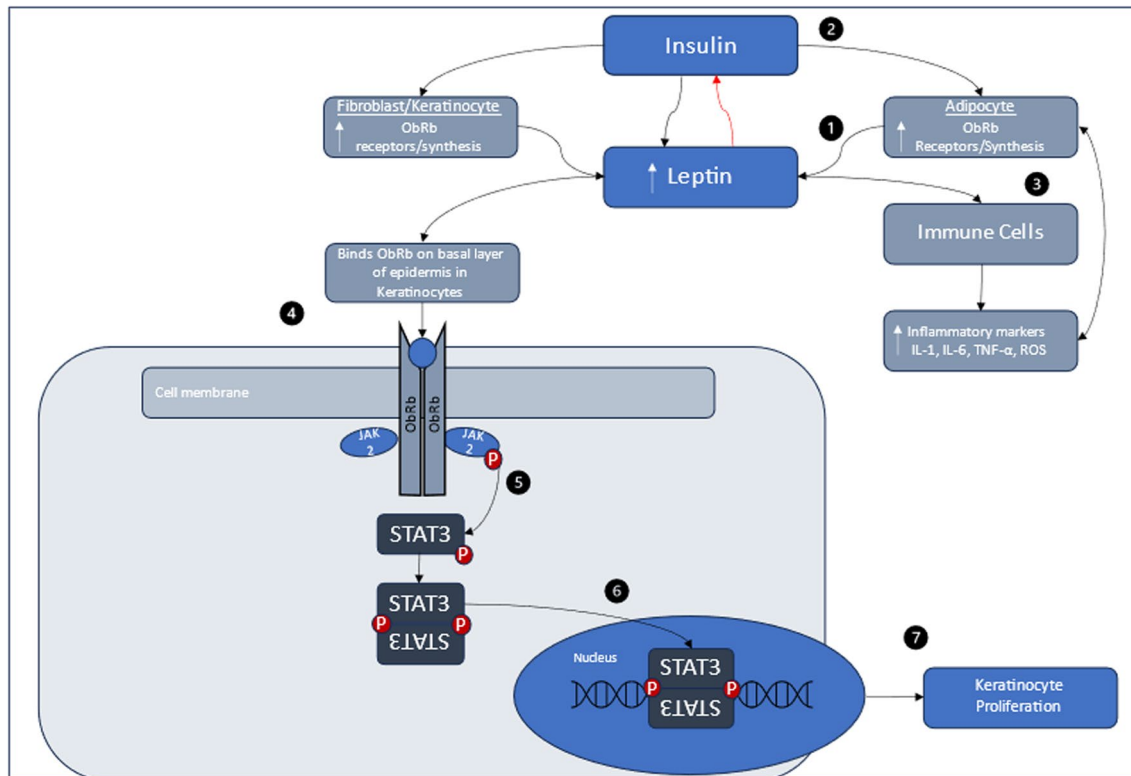


Leptin also plays a role in insulin resistance as it interacts with insulin receptor substrate 1 (IRS1) and IRS2, promoting insulin sensitivity and reducing insulin levels [30]. However, during obesity, the elevated leptin levels can act as a pro-inflammatory cytokine, potentially leading to insulin resistance [31, 32]. Insulin resistance leads to increased insulin levels, which, in turn, further enhances leptin synthesis and release [29]. This creates a feedforward mechanism involving obesity, leptin, and insulin, resulting in a state of hyperinsulinemia and hyperleptinemia (Fig. 3).

While leptin and receptors are produced in adipocytes, they are also expressed in various other tissues, including keratinocytes and fibroblasts [33–37]. The leptin receptors in these skin cells are similar to those in adipocytes and the hypothalamus. Insulin increases the expression of leptin receptors in fibroblasts, suggesting that leptin may have auto-crine and paracrine functions [33, 34]. Leptin can stimulate the proliferation of keratinocytes and fibroblasts, promote epithelialization, and enhance collagen synthesis by binding to ObRb receptors in the skin and modulating the JAK/STAT (Fig. 4), and ERK pathways [33, 35, 36]. Additionally, leptin receptors in AN-affected tissue are upregulated [37]. The increased proliferation induced by leptin, along with the proliferation stimulated by IGFR, likely contributes to the development of AN. These findings are supported by the positive correlation between increased leptin levels and AN compared to obesity alone [38–41].

**Fig. 3** Acanthosis Nigricans and the development of hyperinsulinemia and hyperleptinemia. The development of obesity can result in insulin resistance, which results in increased serum levels of insulin. Insulin increases leptin production and leptin receptors throughout the body. Elevated levels of leptin can further develop insulin resistance resulting in a state of hyperinsulinemia and hyperleptinemia





**Fig. 4** Acanthosis Nigrans and the leptin signaling pathway. 1. Adipocytes are the main source of Leptin synthesis, but many other tissues synthesize leptin including fibroblasts and keratinocytes. 2. Insulin increases leptin synthesis and leptin receptors (ObRb) in the tissues. Leptin in turn decreases insulin synthesis and secretion from the pancreatic beta cells. 3. Leptin binds to immune cells causing them to release proinflammatory markers. In turn these stimulate adipocytes to synthesize more leptin. 4. Leptin binds to Leptin receptors (ObRb) on keratinocytes. 5. The binding of leptin activates JAK2 Tyrosine Kinases which then phosphorylate STAT3. 6. The phosphorylated STAT3 dimerize and transport to the nucleus to regulate their target genes

### 3 Treatment (Table 1)

The primary approach to treating AN is addressing the root cause. As most cases of AN are associated with obesity, hyperinsulinemia, and hyperleptinemia, weight loss is effective in reducing the severity of the disease [20, 42, 43]. Weight loss improves insulin resistance, leading to decreased insulin levels and a reduction in inflammatory markers such as TNF- $\alpha$  [44]. Additionally, weight loss results in decreased adipocytes, which subsequently lowers leptin levels as there is a direct correlation between leptin levels and obesity [25–27]. Another potential approach worth considering is focused on reducing leptin levels in patients. Lowering plasma leptin levels restores leptin sensitivity in the hypothalamus, leading to improved insulin sensitivity and weight loss [45]. Although there are currently no approved therapies targeting leptin levels for AN, ongoing research may shed light on potential future treatments.

Topical treatments have been a first-line therapy for AN. Retinoids, vitamin D analogs, keratolytic creams, and chemical peels are commonly used, with retinoids being the most utilized [20, 46]. Various retinoids are effective in treating AN lesions, but continuous use is often required to prevent relapse [47]. In case reports, topical vitamin D analogs were effective in treating AN, as vitamin D reduces keratinocyte proliferation and may, therefore, be beneficial in hyperproliferative skin diseases [48–51].

Chemical peels work by destroying the epidermis, which then requires repair and rejuvenation of the skin [20]. Chemical peels with trichloroacetic acid decrease papillomatosis and hyperpigmentation within one month of use and show improvement in the appearance of AN [52]. Other peels, including glycolic acid and salicylic acid, also show improvement, but may not be effective as other therapies [53].

Laser treatments have emerged as a promising option for AN management and are more effective than topical therapies [54–57]. Lasers can be ablative or non-ablative, and they can also be fractionated or non-fractionated. Ablative lasers are the

**Table 1** Comparative Analysis of Treatments for Acanthosis Nigricans: Effectiveness and Considerations

| Treatment                 | Description   | Effectiveness   | Considerations  |
|---------------------------|---|---|---|
| Topical Retinoids         | Promote skin cell turnover and reduce keratinocyte proliferation, commonly used as first-line therapy for AN  | 90.0% and 85.0% of participants had more than 75% improvement                     | Continuous use is often required to prevent relapse. Some patients may experience skin irritation or dryness as a side effect               |
| Topical Vitamin D Analogs | Reduces keratinocyte proliferation  | Effective in some case reports in treating AN                                     | May take several weeks to see improvement. Side effects may include skin irritation and sensitivity to sunlight                             |
| Chemical Peels            | Exfoliate the outer skin layers, promoting regeneration and reducing pigmentation. Includes trichloroacetic acid, glycolic acid, and salicylic acid   | Significant improvement in skin texture and appearance                            | May cause redness, peeling, and sensitivity; multiple sessions often required. Less effective than laser treatments                         |
| Laser Treatments          | Target affected areas, promoting skin rejuvenation<br>Ablative laser includes, fractional carbon dioxide.<br>Non-ablative lasers includes long-pulsed alexandrite, fractional and fractional 1550-nm erbium fiber laser | Highly effective, surpassing outcomes of topical treatments                       | Costly; multiple treatments may be necessary. Patients may experience temporary redness, swelling, or mild discomfort after treatment       |
| Isotretinoin              | An oral retinoid reserved for resistant or extensive AN cases. Reduces skin oil production and keratinocyte proliferation   | Improves AN lesions during treatment  | Multiple side effects, including pruritus, epistaxis, erythema, dryness, and cheilitis. Relapses common after discontinuation               |
| Metformin                 | An insulin sensitizer used for AN associated with insulin resistance and obesity, reducing glucose levels and improving insulin sensitivity   | Effective in reducing AN lesions, especially with insulin resistance and obesity  | Generally well-tolerated; side effects include gastrointestinal symptoms such as nausea or diarrhea. Suitable for diabetic patients with AN |
| Thiazolidinediones        | Lower insulin levels and improve insulin sensitivity  | Potential benefit; improvement noted with DPP-4 inhibitors                        | Not extensively studied for AN alone; side effects include weight gain, edema, and increased risk of heart failure                          |
| GLP-1 Receptor Agonists   | Improve weight loss and reduce insulin resistance, contributing to the management of AN   | Increases weight loss and improves insulin resistance which may reduce AN lesions | Side effects may include gastrointestinal issues and risk of pancreatitis   |

most aggressive as they remove the epidermal skin layer, resulting in more dramatic treatment effects [58]. Non-fractionated lasers treat the entire projected surface area of the skin, whereas fractionated lasers treat smaller sections of skin within a target area [58]. The ablative fractional carbon dioxide laser is very effective in treating AN and is more effective than chemical peels and creams [54, 56]. Non-ablative lasers, such as the long-pulsed alexandrite laser and fractional 1550-nm erbium fiber laser, are not as aggressive as the carbon dioxide laser, but are also effective in treating AN lesions [20, 53]. While laser therapy is effective, it can be costly, and multiple treatments may be necessary.

Systemic treatments for AN are generally reserved for lesions that are resistant to topical treatments or those that are too extensive for localized therapy. Oral therapies, such as isotretinoin, metformin, and melatonin, have been explored with varying results [19]. Isotretinoin and related oral retinoids have similar results to topical retinoids, with lesions improving during treatment but relapsing after discontinuation [47, 59]. However, due to the numerous side effects associated with oral retinoids, they are generally not considered useful for treating AN.

Metformin and other insulin sensitizers have some effectiveness in the treatment of AN associated with insulin resistance and obesity. These medications work by reducing glucose levels and reduce the number of AN skin lesions [47, 60]. In a recent small double-blind randomized controlled trial comparing metformin to an OTC combination medicine of alpha-lipoic acid, biotin, calcium pantothenate, and zinc sulfate for the treatment of AN, both medications improved the AN lesions [61]. Considering metformin's safety profile and widespread use for diabetes management, it is a reasonable option for the additional benefit of treating AN, especially in obese patients.

Other diabetic drugs may also hold promise for AN. Thiazolidinediones effectively lower insulin levels and are more effective in treating diabetes compared to metformin [62]. While thiazolidinediones have not been extensively studied specifically for AN treatment, there is evidence suggesting their potential benefit. A combination treatment of DPP-4 inhibitors and thiazolidinediones improve AN lesions [63].

Glucagon-like peptide-1 (GLP-1) receptor agonists may also be useful for AN treatment. These agents improve weight loss and insulin resistance, both of which contribute to the pathogenesis of AN [64]. The benefit of enhancing glycemic control and promoting weight loss makes GLP-1 receptor agonists a promising option for managing AN in patients with diabetes. Further research is needed, however, as we identified no studies on the subject.

## 4 Discussion

### 4.1 Differential diagnoses

There are typical findings in AN that can be quickly recognized. The velvety hyperpigmented and hyperkeratotic lesions appear mostly in the axillae, neck, and body folds [20]. There can also be atypical locations including the scalp, face, hands, over joints and anywhere else on the body [20]. At times the lesions can mimic the appearance of psoriasis and with psoriasis being tied to metabolic syndrome, obese patients may present with both diseases. Psoriasis can be differentiated from AN by its raised, well-demarcated lesions that are typically erythematous and more inflamed. Another mimic may be terra firma-forme dermatosis, which appears as dirt-like lesions, typically on the face, neck, and ankles. The lesions can easily be distinguished from AN by treating by rubbing with alcohol wipes [65]. Other lesions that can mimic AN include, melasma, atopic dermatitis, lichen simplex chronicus, post-inflammatory hyperpigmentation, and seborrheic keratosis, and several others [20].

Rarely AN can be a cutaneous manifestation of various malignancies, particularly gastric adenocarcinoma [1, 20]. Malignant AN can present similarly to benign AN, but malignant AN can have a more abrupt onset, involve more of the oral cavity, and have intense pruritus [1]. This should be a high suspicion, especially when the patient presents with constitutional symptoms and AN; however, malignant AN can present before any clinical signs of malignancy appear.

## 5 Metabolic syndrome

AN is positively correlated with meeting the criteria for metabolic syndrome of hyperglycemia, high BMI, increased waist circumference, high triglycerides, and hypertension [11]. Meeting 3 of the 5 criteria for metabolic syndrome doubles the risk of cardiovascular disease and increases all-cause mortality [66]. The quick recognition of AN's significance in cardiovascular risk assessment could aid in the early detection and prevention of cardiovascular diseases, leading to improved patient outcomes.

AN has potential as an early screening tool for metabolic diseases such as insulin resistance and subclinical atherosclerosis [42]. Given the association of AN with high levels of insulin, BMI, and leptin, there is an increased risk for cardiovascular diseases. Insulin has negative cardiovascular implications as insulin resistance can increase the risk of myocardial infarction by 2 to 4 times [67]. Similar to how insulin and IGF lead to changes in the skin, high levels of insulin can bind to receptors on the heart and lead to cardiovascular remodeling and heart failure [68]. Similarly, insulin resistance can have negative effects on the vasculature. Under normal conditions, Insulin binds to vasculature endothelium receptors, resulting in nitric oxide release for vasodilation [69]. Insulin resistance disrupts this process, causing adverse inflammatory effects such as mitochondrial dysfunction, oxidative stress, and protein kinase C activation which leads to endothelial dysfunction, impaired vasodilation, arterial narrowing, and atherosclerosis [69].

## 5.1 Screening for metabolic and cardiovascular risk factors

Considering that AN screening is easily performed and noninvasive, it could serve as an affordable and useful screening tool. AN has already been used as a screening tool in children and adolescents to identify those at risk of developing type 2 diabetes [9, 70, 71]. This screening could be further expanded to include cardiovascular disease. Presentation of AN could warrant referral to primary care for measurements of blood pressure, BMI, waist circumference, glucose levels, and a lipid panel which are all determinants of metabolic syndrome. Measurements of insulin resistance could also be considered, including homeostasis model assessment of insulin resistance (HOMA-IR), fasting insulin level, glucose/insulin ratio, etc. By combining the simplicity of AN screening with a comprehensive assessment of metabolic and cardiovascular risk factors, patients will have improved health outcomes as many patients presenting to dermatology have many unmet preventative healthcare needs [72].

## 6 Conclusion

AN is not simply a cosmetic issue. When patients present with AN it may be an indication that they may benefit from referring to a primary care to discuss screening for metabolic disease, exercise, diet, and the cardiovascular risks associated with AN. Treatment options attacking the root cause of AN, including improving metabolic health and weight loss are effective in treating the disease [21, 46, 47]. Cosmetic treatments have been used with good but temporary results. Newer treatments like SGLT2 inhibitors may show promise for treating AN as it helps with insulin resistance, obesity, and improves cardiovascular outcomes. Further research is needed, however, on the specific effects of SGLT2 inhibitors on AN as we identified no studies on the subject.

**Author contributions** E.E. wrote the main manuscript text and abstract, prepared Figs. 1, 2, 3, 4, and Table 1. S.F. Edited the main manuscript text All authors reviewed the manuscript

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** Feldman has received research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Quri-ent, Forte, Arena, Biocon, Accordant, Argencx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, BMS, Ono, Microcos, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. He is founder and part owner of Causa Research and holds stock in Sensal Health. The authors declare no competing interests.

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