Addressing the cardiovascular implications of acanthosis nigricans: what a dermatologist needs to know

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Abstract

Background: Acanthosis nigricans (AN) is a dermatologic skin condition that is often overlooked in its role as an indicator of underlying cardiovascular disorders. Recognizing the importance of AN beyond its cosmetic concerns is crucial for improving patient outcomes.

Objective: Provide a review of AN and what every dermatologist should know of its underlying cardiovascular risk.

Methods: A literature search through PubMed was performed. Terms used were "Acanthosis Nigricans," "hyperinsulinemia," "cardiovascular disease," "diabetes," "insulin resistance,". Further articles were found using source materials from included references. Inclusion criteria involved studies showing the association between AN and cardiovascular risks, with a specific focus on obesity and insulin resistance.

Results: Acanthosis nigricans increases risks of obesity and insulin resistance as individuals with AN exhibited a 2.6-fold higher likelihood of insulin resistance, independent of other factors. Acanthosis nigricans surpassed other risk factors in classifying individuals at risk for type two diabetes and cardiovascular disease.

Conclusions: Recognizing the association of AN with cardiovascular disease provides an opportunity for early intervention, focusing on weight management and underlying metabolic disorders to improve both cosmetic concerns and cardiovascular health. Dermatologists should consider AN as a signal that prompts referral for a thorough assessment for associated metabolic diseases.

Keywords: acanthosis nigricans, cardiovascular disease, leptin insulin resistance, obesity, surgery

Introduction

Acanthosis nigricans (AN) is a dermatological skin condition characterized by the presence of thickened hyperpigmented plaques with indistinct borders, predominantly found bilaterally in intertriginous folds such as the axilla, neck, and groin. The significance of AN extends beyond cosmetic concerns; it exhibits a strong correlation with metabolic disorders and, increased cardiovascular risks. Acanthosis nigricans has various etiologies, including malignancies, endocrine disorders, and obesity. Early recognition of these underlying conditions may help prevent their progression and enhance patient outcomes. This review aims to explore those underlying conditions and the cardiovascular implications of AN.

Discussion

Pathophysiology

The development of AN has been strongly linked to obesity, with a direct correlation between disease prevalence and body mass index. Among adolescents, AN prevalence reaches as high as 66% for those above 200% of their ideal body weight and 61.54% for obese adolescents [12]. In clinics specializing in adult obesity, AN prevalence reaches 74% [3]. Children with AN exhibited higher body fat mass compared to those without [4]. Another marker

associated with AN is insulin resistance. Individuals with AN are 2.6 times more likely to have insulin resistance than those without [5]. In adolescents, AN can serve as an independent marker for insulin resistance [6]. Additionally, the presence of AN is linked to a two-fold higher likelihood of type two diabetes compared to individuals without AN [7].

One proposed mechanism for the development of AN involves hyperinsulinemia. Individuals with obesity have even higher levels of insulin owing to increased plasma free fatty acids and adipokines released from adipose tissue [8]. This impairs glucose transport resulting in insulin resistance. The link between hyperinsulinemia with insulin resistance and AN is mediated via the insulin-like growth factor 1 (IGF1) pathway. Elevated insulin levels lead to an increase in IGF1 levels in the serum [9,10]. Excess insulin can release IGF1 from its binding proteins, resulting in elevated free IGF1 in the serum. This surplus of IGF1 can directly stimulate IGF1 receptors on keratinocytes and fibroblasts, initiating a signaling cascade that culminates in proliferation, hyperpigmentation, and acanthosis [11,12].

Implications of obesity and insulin resistance

Physicians should not only consider AN in individuals with obesity for cosmetic reasons but also to signal the need to assess for underlying metabolic diseases that carry associated cardiovascular risks (**Table 1**). Obesity increases the risk of heart disease and is an independent marker for cardiovascular disease [13]. Furthermore, obesity independently increases other cardiovascular disease risk factors, including hypertension, dyslipidemia, metabolic syndrome, type two diabetes mellitus, and inflammation [14].

Acanthosis nigricans could serve as an early indicator for cardiovascular disease as it may be a signal for subclinical atherosclerosis [15]. Patients with AN had increased carotid intima-thickness compared to those without [16]. Patients with AN had a high prevalence of abnormal glucose tolerance and hyperinsulinemia. In addition, euglycemic patients with hyperinsulinemia had a cluster of risk factors for cardiovascular disease [17]. Insulin resistance and high insulin levels also elevate the risk of heart disease and diabetes, leading to a 2 to 4-fold increase in myocardial infarction risk [18,19]. Furthermore, insulin resistance increases the relative risk of developing cardiovascular disease [20]. Despite its well-known role in glucose uptake, functions of insulin extend throughout the body, including the heart, vasculature, and skin.

In normal physiological conditions, insulin binds to receptors on the endothelium of the vasculature, triggering signaling pathways involving P13K and

Table 1*: Assessment and diagnostic tools for acanthosis nigricans.*

Assessment/diagnostic test	Criteria/method
Atherosclerotic cardiovascular disease risk estimator	Calculates the risk for atherosclerotic cardiovascular disease risk estimator based on age, gender, blood pressure, medical history, familial risk factors, and lipid panel results (triglycerides, LDL, HDL levels) Results guide treatment options, including lifestyle modifications and statin therapy LDL levels of ≥190mg/dl automatically qualify for statins
Metabolic syndrome assessment	Identifies patients at risk for metabolic syndrome, which increases the likelihood of cardiovascular disease and type 2 diabetes Presence of three or more of the following criteria: 1. Elevated waist circumference 2. Triglyceride levels ≥150mg/dl 3. Reduced HDL-C levels (males: <40mg/dl; females: <50mg/dl) 4. Elevated blood pressure (systolic ≥130mm Hg or diastolic ≥85mm Hg) 5. Fasting glucose levels ≥100mg/dl
Insulin resistance assessment	Fasting plasma glucose : values between 100-125mg/dl indicate insulin resistance and prediabetes; ≥126mg/dl indicates diabetes Oral glucose tolerance test : values between 140-199mg/dl indicate prediabetes; ≥200mg/dl indicates diabetes Hemoglobin A1C: threshold of 6.5% indicates diabetes; values >5.5% indicate increased risk of diabetes [32]

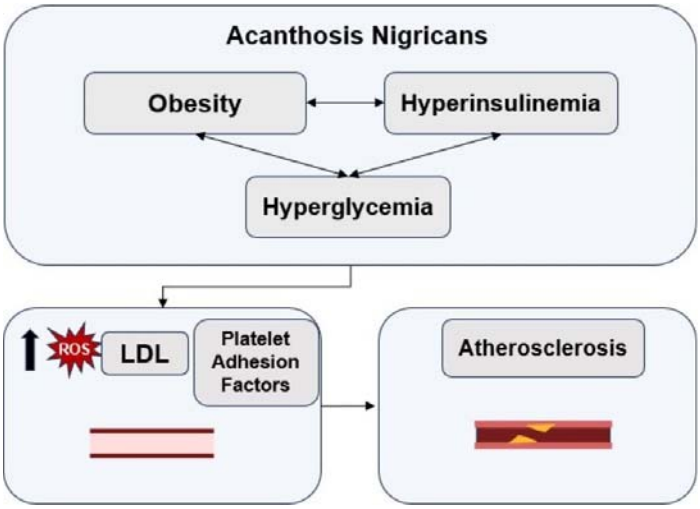

Figure 1. *Acanthosis nigricans and the associated atherosclerosis.*

Obesity, hyperinsulinemia, and hyperglycemia all synergistically increase inflammatory markers and reactive oxygen species (ROS). These changes lead to endothelial dysfunction, impaired vasodilation, and narrowing of the artery. High levels of insulin also lead to increased levels of platelet adhesion factors and LDL which ultimately enhances development of atherosclerosis.

AKT. This leads to nitric oxide release, promoting vasodilation and exerting anti-inflammatory effects [19]. However, insulin resistance disrupts this process through a variety of factors, including hyperglycemia, resulting in a range of adverse effects. Prolonged hyperglycemia induces mitochondrial dysfunction, increases oxidative stress, and activates protein kinase C. These factors collectively lead to endothelial dysfunction, impaired vasodilation, and arterial narrowing (**Figure 1**), [21]. Insulin resistance also amplifies the risk of atherosclerosis [22,23]. Elevated blood glucose levels trigger the production of mitochondrial reactive oxygen species, leading to increased expression of inflammatory and adhesion factors, oxidized low-density lipoprotein formation, and accelerated atherosclerosis (**Figure 1**), [23].

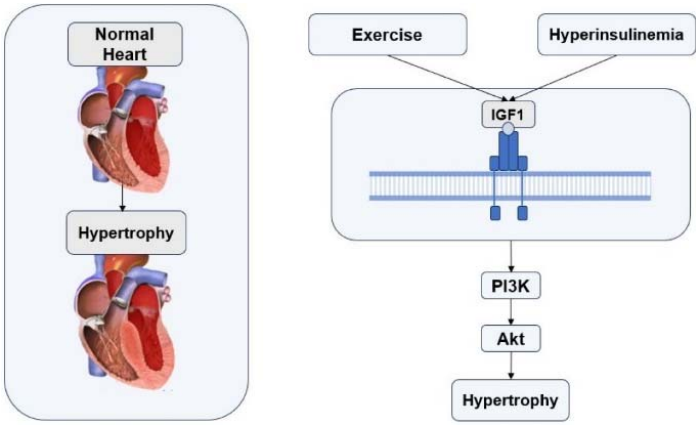

Figure 2. *Acanthosis nigricans and cardio-remodeling.*

Exercise induces physiological stress on the heart and activated IGF1 receptors. These receptors lead to physiological cardiac remodeling and eccentric hypertrophy which is healthy for the heart. A state of hyperinsulinemia can also lead to increased activation of IGF1 receptors that can chronically activate the receptors. The over activation of the IGF1 receptors causes a cascade of signaling pathways to be activated and may be one of the reasons why diabetics and patients with insulin resistance develop diabetic cardiomyopathy and ventricular hypertrophy.

In the heart, obesity, diabetes, and insulin resistance play similar roles as in vasculature. Hyperglycemia, hyperinsulinemia, and hypertriglyceridemia lead to the accumulation of toxic metabolites and reactive oxidative species within cells, triggering pathological signaling pathways. This cascade results in inflammation, disrupted calcium signaling, and mitochondrial dysfunction, ultimately contributing to diabetic cardiomyopathy [24].

IGF1 also plays a role in cardiac hypertrophy, in a process that is like the development of AN. At normal levels IGF1 binds to receptors on the heart and induces physiologic hypertrophy and has cardioprotective effects [25-27]. In a hyper-insulin state, however, IGF1 levels are increased and overactivated. This overactivation leads to hypertrophy beyond beneficial levels and may be a mechanism for left ventricular hypertrophy or diabetic cardiomyopathy in metabolic syndrome (**Figure 2**), [28,29].

Diagnostic workup

With the metabolic implications of AN, further workup is warranted to guide treatment and accurately assess the patient's risk profile (**Table 1**). A commonly used risk assessment is the American Heart Association and the American College of Cardiology's atherosclerotic cardiovascular disease (ASCVD) risk estimator [30]. This tool includes various factors such as age, gender, blood pressure, medical history, familial risk factors, and lipid panel results including triglycerides, LDL, and HDL levels. Utilizing the ASCVD risk estimator enables clinicians to stratify the patient's risk of ASCVD and recommend appropriate treatment options, with a focus on lifestyle modifications and lipid-lowering medications like statins [30]. This is a simple and cost-

effective option for clinicians to assess the cardiovascular risk of AN patients.

Including metabolic syndrome assessment in the diagnostic workup of AN patients is useful owing to their heightened risk of developing this condition, which increases the likelihood of cardiovascular disease and type two diabetes [14]. Metabolic syndrome is characterized by the presence of three or more of the following criteria: elevated waist circumference (with specific thresholds tailored to population and country), triglyceride levels equal to or exceeding 150mg/dl, reduced HDL-C levels below 40mg/dl in males and below 50mg/dl in females, elevated blood pressure indicated by a systolic reading of 130mm Hg or higher and/or a diastolic reading of 85mm Hg or higher, and fasting glucose levels of 100mg/dl or greater [31].

In addition to a cardiovascular risk assessment, evaluating insulin resistance in AN patients is performed through various tests, including fasting plasma glucose, oral glucose tolerance test, and hemoglobin A1C. Fasting plasma glucose measures plasma glucose levels after at least 8 hours of fasting; values between 100 and 125mg/dl indicate insulin resistance and prediabetes and values ≥126mg/dl indicate diabetes [32]. Oral glucose tolerance test involves administering 75g of glucose to the patient, followed by measuring plasma glucose levels two hours later; values between 140 and 199mg/dl indicate prediabetes and values ≥200mg/dl indicate diabetes [32]. Hemoglobin A1C reflects average blood glucose levels over the past three months, with a threshold of 6.5% indicating diabetes and values above 5.5% indicating increased risk of developing diabetes [32]. Additionally, indices such as the homeostasis model assessment for insulin resistance and the quantitative insulin sensitivity check index provide further insights into insulin sensitivity and pancreatic β-cell function. However, firm cut off values have not been established [33].

Acanthosis nigricans is predominantly associated with metabolic disorders, but it can rarely manifest as a paraneoplastic phenomenon, often linked to adenocarcinomas such as gastric adenocarcinoma [34]. Malignant AN differs from metabolic AN in its abrupt onset, rapid progression, and occurrence in unusual sites such as the oral mucosa. In addition, paraneoplastic AN tends to occur in older and non-obese patients [34]. Additional skin findings in malignant AN may include mucosal and cutaneous papillomatosis, tripe palms, and Leser-Trélat sign [34,35]. Malignant AN may also present with constitutional symptoms, such as unexplained weight loss, fever, fatigue, and gastrointestinal upset [35]. If malignant AN is suspected, a tailored workup is necessary as it depends on the underlying malignancy; there is no established workup for malignant AN cases.

Treatment implications

Acanthosis nigricans is more than a cosmetic concern. Acanthosis nigricans is a potential indicator of underlying metabolic conditions. For individuals with obesity who suffer from AN, addressing weight management becomes important not only to improve the AN but also to mitigate metabolic and heart related complications. Treatment of AN should focus on the underlying disease pathology and individuals presenting with AN should be screened for obesity, insulin resistance, and heart disease. Actions should be taken to address the underlying disorders (**Table 2**). Obesity-related AN should focus primarily on weight loss which can normalize hyperinsulinemia and thus treat AN [8]. Referral to specialized weight management clinics should be considered for complex patients with multiple medical comorbidities. If the patient is not responding to first-line therapies, referral for consideration of bariatric surgery may be appropriate. Interventions targeting insulin resistance, weight loss, and exercise hold promise and show benefit in managing AN and reducing the associated heart disease. Weight loss has the most benefit as it not only results in improvement of AN, but it also reduces the cardiovascular risks associated with obesity, diabetes, and insulin resistance [36-39].

Weight reduction can be achieved by various methods and may require the use of combination therapy. The target weight reduction goal that has been associated with improvement in insulin resistance, which is a driver of AN, is 5-10% of the initial body weight [40,41]. This amount of weight loss can be achieved using comprehensive lifestyle

Table 2. *Acanthosis nigricans (AN) recognition and interventions.*

Obesity	Recognize the increased incidence of AN with increased body mass and obesity Identify AN in intertriginous folds	Assess BMI and waist circumference Encourage weight management and exercise Consider GLP-1 agonists for potential benefits
Cardiovascular risks	Consider AN as marker for subclinical atherosclerosis and cardiovascular disease Recognize AN as signal for obesity and diabetes and their impact on cardiovascular disease	Evaluate lipid profile Evaluate family history of cardiovascular disease Monitor blood pressure Consider GLP1 agonists and SGLT2 inhibitors
Insulin resistance	Recognize AN's role as an early indicator for metabolic diseases Understand AN's link to hyperinsulinemia and IGF1 Recognize the connection between Type 2 diabetes and AN	Oral glucose tolerance test HOMA-IR[a] score which stands for Homeostatic Model Assessment for Insulin Resistance is a tool to determine if insulin resistance is present. The calculator takes into account insulin and glucose levels. Another similar tool is QUICKI[b] which stands for Quantitative Insulin Sensitivity Check Index Evaluate fasting blood glucose, insulin levels, and HbA1C levels Consider insulin sensitizers (metformin, pioglitazone) Consider GLP1 agonists for potential benefits If malignancy associated AN is suspected then a CBC is recommended

[a]HOMA-IR is calculated as G_0 (mmol/l) × I_0 (μU/ml)/22.5 or as G_0 (mg/dl) × I_0 (mU/l)/405. where I_0 is fasting insulin and G_0 is fasting glucose. Interpretation can vary but levels of 2 or greater may be interpreted as insulin resistance.
[b]QUICKI is used to determine insulin sensitivity. It calculated as 1/[log(I_0) + log(G_0). Where higher values equal better insulin sensitivity.

interventions, anti-obesity medication (AOM) in conjunction with lifestyle modification, and surgical treatment. Comprehensive lifestyle interventions include a prescribed calorie restriction of 500-7500kcal below estimated energy needs, 150 minutes of moderate levels of physical activity weekly, and behavioral counseling that will typically result in 6-8% weight loss at 12 months [42]. For those who are not responding to this type of intervention or have previously had limited treatment response, initiation of AOM is a recommended next step. First generation AOM, which includes orlistat, naltrexone/bupropion, and phentermine/topiramate typically results in 5-10% body weight reduction whereas the newer class of AOM that includes GLP1-agonists typically results in 10-20% body weight reduction [43]. New pharmacotherapy that will address the treatment gap between current AOM and bariatric surgeries are awaiting FDA approval or in phase 2/3 clinical trials. Bariatric surgery compared to AOM leads to the highest total weight reduction whereas the various surgeries range between 25-35% of total body weight reduction [44]. These surgeries in order of greatest weight reduction include vertical sleeve gastrectomy, Roux-en-Y gastric bypass, and duodenal switch. Bariatric surgery should be considered in individuals with BMI of 40 or greater with no comorbidities, BMI of 35 or greater with obesity associated comorbidity, and failure of previous nonsurgical weight loss attempts that can include commercial programs or supervised medical weight management programs.

Theoretically, diabetic medications can be used to treat AN, but there are limited studies/data on various diabetic medications and AN. Metformin, a frequently prescribed insulin sensitizer, has multiple benefits. Beyond its recognized role in diabetes control, metformin reduces AN lesions by improving hyperinsulinemia. This occurs by reducing glucose and increasing insulin sensitivity peripherally while also providing cardioprotective effects [45-47]. A combination of metformin and thiazolidines or dipeptidyl peptidase-4 inhibitors, such as sitagliptin, alone improved AN in reports. Another insulin sensitizer, pioglitazone, is effective in treating diabetes and AN. However, it increases the likelihood of developing heart failure and should be used

cautiously in patients with symptomatic heart failure [48-50]. Sodium glucose co-transporter 2 inhibitors may also be beneficial as they treat diabetes and are cardio-protective, but they have not yet been studied for AN [51,52].

Glucagon-like peptide 1 receptor (GLPR1) agonists may also offer benefits, as they improve weight loss, insulin resistance, and cardiovascular outcomes [53-55]. Glucagon-like peptide 1 receptor agonists belong to the family of incretin hormones, which are transiently released after eating and bind to receptors throughout the body, exerting a range of effects. Once released, these hormones can enhance type two diabetes management by stimulating insulin release and increasing glucose uptake by cells, even in insulin-resistant states [56]. Furthermore, GLPR1agonists promote weight loss by stimulating brown fat metabolism, slowing gastric emptying, and enhancing satiety [54-56]. Given their potential impact on insulin resistance and weight loss, GLPR1agonists appear promising.

Conclusion

Patients seeking dermatological care for AN predominantly have concerns related to its cosmetic appearance rather than the underlying metabolic disorders. Limiting treatment solely to dermatological interventions falls short of addressing the broader health implications for these individuals. Dermatologists should educate the patients about the associated risks of AN and refer to primary care and relevant specialties to ensure proper management of the patients.

Although a connection exists between AN and cardiovascular disease from the associated risk factors, notably obesity and insulin resistance, we found no published studies on the direct correlation between AN and cardiovascular disease. But with the underlying pathology of AN, and the associated risks of the disease, individuals presenting with AN should be screened for obesity, insulin resistance, and heart disease; actions should be taken to address the underlying disorders (**Table 1**).

Acanthosis nigricans is a distinctive dermatological skin condition with implications that extend beyond visible skin manifestations. With its strong association with obesity and insulin resistance, AN may be an early indicator of underlying metabolic diseases. The pathophysiological mechanisms involving hyperinsulinemia and, IGF1 and their impact on their development of AN and heart failure underlie the risks of this disease and its cardiovascular implications. Furthermore, the inflammatory state of hyperinsulinemia, hyperglycemia, and obesity damages the endothelial tissue in the vasculature and results in narrowed and atherosclerotic vessels. Recognizing these features and the consequences of the disease may be helpful for early recognition, thus, improving patient outcomes.

Potential conflicts of interest

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, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, BMS, Ono, Micreos, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. He is founder and part owner of Causa Research and holds stock in Sensal Health. The remaining authors declare no conflicts of interest.

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