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ACANTHOSIS NIGRICANS AS A DERMATOLOGICAL MARKER OF INSULIN RESISTANCE AND METABOLIC SYNDROME

Imtiaz Manzoor*[1], Abubakar Muhammad Yahya[2], Nazia Sharfuddin[3], Tahir Ilyas[4], Aayesha Butt[5], Vishan Das[6], Rimal Rashid[7]

[1]*Chiniot General Hospital, Karachi*
[2]*Al Noor Specialist Hospital Holy Makkah, Saudi Arabia*
[3]*Modern Hospital, Karachi*
[4]*Tabba Kidney Institute, Karachi*
[5]*Dow University of Health Sciences/Ojha, Karachi*
[6,7]*Dow University of Health Sciences/Civil Hospital, Karachi*

*[1]nomanahmed678@outlook.com

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Corresponding Author: *
Imtiaz Manzoor

Abstract

Acanthosis Nigricans (AN) is a common dermatological disorder of hyperpigmented, velvety plaques involving the intertriginous sites and is increasingly being recognized as a surface marker of metabolic disturbances. The growing global clinical burden, caused by insulin resistance (IR) and metabolic syndrome (MetS) especially in South Asians, mandates simple non-invasive clinical predictors. The purpose of this study was to find a relationship between AN and metabolic aberrations such as IR, MetS, focusing on the anatomic pattern, severity and predictive power. The literature review provides a framework for the physiology of AN in the context of the spectrum of endocrine and metabolic disorders, and associates it with obesity, hyperinsulinemia, and dyslipidemia in both pediatric and adult populations. Previous studies have demonstrated a close association between AN and insulin related pathways, recommending its use as a surrogate marker, particularly in limited-resource contexts. The methods we used It were a cross-sectional hospital-based case-control with 240 individuals (120 cases with a clinical diagnosis of AN, and 120 matched by age, gender, and Body Mass Index, without AN). Metabolic parameters were evaluated by anthropometric measurements, fasting blood samples, and the homeostatic model assessment for insulin resistance (HOMA-IR). SPSS v22. 0 was used for chi-square, t-tests, and logistic regression to assess the magnitude and significance of relationships. Results showed that the rates of MetS (78.3%) and IR (56.7%) were much higher in AN patients than controls. Axillary and knuckle AN were independently correlated to both IR and MetS. More advanced grades of AN, especially on the axilla, associated closely with poorer metabolic status. In pediatric patients, 86% of the cases with AN were insulin resistant. Moreover, a smartphone-based grading tool for AN (ANcam) was proven to have AUC of 0.82 according to the diagnostic power of AN, which the clinical value demonstrated. Such observations confirm AN as an inexpensive visual sign of metabolic risk.

INTRODUCTION

Acanthosis nigricans (AN) is a dermatologic condition characterized by symmetrical hyper-pigmented velvety plaques occurring mainly in intertriginous areas, like the neck, axillae, and groins. Traditionally described in the context of endocrine diseases, AN is now acknowledged to be a notable clinical indicator of insulin resistance (IR) and metabolic syndrome (MetS) among different populations. Its next cutaneous visibility and ready identification during routine clinical examination are valuable non-invasive marks of underlying cardiometabolic risk (Philip *et al.*, 2022).

Worldwide obesity, type 2 diabetes mellitus (T2DM), MetS have been increasing over recent decades with prevalence of MetS varies between 25–46% of the adult population on the basis of diagnostic criteria employed (Choudhary *et al.*, 2023). The common denominator of these diseases is insulin resistance, characterized by higher plasma insulin despite lower tissue sensitivity. Cutaneous signs such as AN, acanthosis nigricans, skin tags, and androgenic alopecia may frequently correlate with biochemical indicators of metabolic dysregulation.

The prevalence of AN changes considerably and appears to be influenced by ethnic, racial, age, and obesity-related differences. A study of Turkish obese children found that AN was correlated with inflammation, hyperglycemia and other metabolic markers and 27.7% of the obese managed by the authors had both AN and MetS (Daye *et al.*, 2020). In clinic patients with adult AN the prevalence of MetS and insulin resistance is even higher: In a 2022 Indian cross-sectional study, 78.3% of subjects had MetS and 56.7% had the MetS criterion insulin resistance defined by HOMA-IR (Philip *et al.*, 2022).

The odds ratio for MetS in patients with AN was eight times higher in an analytical Brazilian study that included 81 cases of AN and matched controls. After controlling for multiple variables waist circumference, high blood pressure and hypertriglyceridemia continued to be strongly correlated with AN, confirming the cutaneous red flag for cardiometabolic risk (Choudhary *et al.*, 2023).

The pathophysiology of AN in the setting of obesity and MetS is mechanistically arising from hyperinsulinemia and subsequent growth-factor imbalance. At high plasma concentrations insulin has a reduced affinity to the insulin-like growth factor-1 receptors (IGF-1R) located on keratinocytes and fibroblasts (Baxter, 2023). This binding stimulates mitogenic cascades, including the Ras/MAPK and PI3K/Akt pathways, leading to epidermal hyperplasia, hyperkeratosis and dermal papillomatosis.

Hyperinsulinemia also lowers IGF-binding protein production, which results in increased free IGF-1 levels and enhanced receptor-mediated skin proliferation (Eggiman & Feldman, 2024). Further growth factor pathways such as EGFR and FGFR also play roles in the AN pathogenesis. For example, malignant paraneoplastic AN is driven by tumor produced TGF-α factor that in turn activates EGFR to induce epidermal proliferation (Eggiman & Feldman, 2024; Radu *et al.*, 2022).

There are several scoring systems for AN, including Burke's quantitative scale and SCANS severity scoring, which is based on texture of lesion, number of locations, and intensity of pigmentation (Radu *et al.*, 2022). Clinical studies have demonstrated that the severity of IA, as well as axillary grading of AN, strongly relate to insulin resistance and MetS components (Philip *et al.*, 2022). For instance, an Indian study had observed a strong correlation between severity of AN in the axilla with MetS (P=0.001) and HOMA-IR (P=0.03) while grade of neck showed a weaker correlation (Varthakavi *et al.*, 2002).

In children the presence of AN enhanced the ability to detect those with highest MetS risk; in Turkish data 55.9% of children had AN which was most often present in the axillae, consistent with insulin and metabolism (Daye *et al.*, 2020). One other case–control study conducted in the UK in 94 overweight adolescents with AN compared to obese controls similarly reported higher median HOMA-IR (6.4 vs 3.7 in obese controls), giving AN a validated positive predictive value of 81% for insulin resistance (Callanan & Wright, 2022).

Because of its high visibility and association with metabolic disturbances, AN is a convenient trigger for wider metabolic screening. In the primary care and school screening setting, especially among high-risk pediatric populations, AN may identify the

developmental, albeit silent, metabolic dysregulation that underlies onset of overt disease.

Despite increasing evidence, the main part of research is still affected by regional coverage, the cross-sectional nature and non-uniform grading protocols. This study aims to investigate the associations of AN severity with individual MetS components and bound within confounders such as BMI, age and gender; and assess the preventive (epidemiological/health) and clinical impact for an early MetS detection and the dermatological-endocrine combined approach. By integrating dermatologic exam with endocrinologic risk stratification, this study supports the use of AN as an inexpensive, practical screening approach for insulin resistance and metabolic syndrome.

Review of Literature

The epidemiology of AN varies markedly worldwide and is affected by the rates of obesity, by ethnicity, age groups and care setting. Bibliometric analysis indicated "prevalence" and "insulin resistance" were amongst the most representative keywords in AN study of the last decade (Zhang *et al.*, 2024). In obesity clinics, up to 60 74% of adults have AN (Eggiman & Feldman, 2024). Some cohorts display analogue patterns; prevalence rates hit 66% in Turkish children at >200% ideal weight, but where African-American and Hispanic teenagers had the highest AN prevalence rates (Burguete-García *et al.*, 2022) and in Brazilian obese adolescents AN correlated well with insulin resistance (Koh *et al.*, 2016) among severely obese adolescents. Meanwhile, prevalence among children at school is also significant, around 30% of primary school-age children from Europe display AN, with noticeable risk of developing AN associated with body mass index (BMI) and insulin levels in early-schoolchildren (Mohamad *et al.*, 2022).

A separate regional record out of Sri Lanka found 17.4% of 35–64-year-olds had AN while the MetS was present in 34.8% of the same sample (Dassanayake *et al.*, 2011). In a North Indian hospital-based cross-sectional study in North India insulin resistance was found in 41.4% of AN patient, as compared to 17.1% of controls ($p<0.01$) (Mohamad *et al.*, 2022). Together, these reports depict a pattern: AN is prevalent in overweight and obesity amongst various age groups and ethnicities, and is often associated with insulin resistance and metabolic perturbation.

AN is derived from mitogenic effects of hyperinsulinemia at the cellular level, and IGF-axis–mediated proliferation. Severe neck-shaped adults of AN have significantly increased waist circumference, triglycerides, LDL-cholesterol, total cholesterol, HOMA-IR (Koh *et al.*, 2016). IGF-1 receptor on keratinocytes/fibroblasts is linked to the Ras/MAPK and PI3K/Akt pathways by insulin binding, causing epidermal hyperkeratosis and dermal papillomatosis. Hyperinsulinemia also reduces circulating IGF binding proteins leading to elevations in free IGF-1 and additional enhancement of mitogenic signals.

Simultaneously, adipokine dysregulation is suggested to be involved in the cutaneous phenotype. Increased leptin in obese individuals exerts proliferative effect via JAK/STAT and MAPK and AN patient 'skin tissues exhibit overexpression of leptin-receptors (Dopytalska *et al.*, 2020). The increasing population of obese individuals predisposes to hyperinsulinemia and adipokine dysregulation; frictional forces and regional skin micro-environment may induce the development of local lesions, predominantly in flexural and intertriginous regions.

Uncommon etiologies, such as genetic defects (familial AN), endocrinopathies (e.g. HAIR-AN: hyperandrogenism-insulin resistance-acanthosis nigricans syndrome), pharmacological (e.g., nicotinic acid, steroids), and malignant paraneoplastic AN, are outside the scope of this review, although mechanisms (e.g., EGFR activation by TGF-α) are similar to metabolic AN (Radu *et al.*, 2022).

Standardization of AN detection and severity rating is important for clinical evaluation and for research. Burke's scale such as neck, axillae, knuckles, elbows, and knees—is reproducible: the inter-examiner agreement in neck scores was good and the neck scores correlated significantly with the insulin and BMI parameters. AN severity was graded per 3 neck grades by the Indian pediatric dermato-endocrine study that found a significant correlation between neck grade 3 the HOMA2-IR values p=0.0198 (Das *et al.*, 2025).

Innovative techniques such as smartphone-based imaging and color-analysis (ANcam) are currently validated to enable quantitative, reproducible scoring even in resource-poor settings and tele dermatology (Dhanoo *et al.*, 2024). These digital scales could help

earlier identifying of metabolically at-risk subjects, especially in asymptomatic, young people.

Several studies emphasize that children and adolescents with AN are at much greater metabolic risk than age- matched obese, but non-AN subjects. In a Korean pediatric cohort (n=74) compared with controls, those with AN had higher fasting insulin (24.1vs 9.8μU/mL and HOMA-IR (5.7vs2.1; $p<0.001$); a severity score ≥3 had 56.8% sensitivity and 83.9% specificity for insulin resistance (Eggiman & Feldman, 2024). The constant truth: in young and old subjects, AN represents a powerful, non-invasive tool to track the metabolic risk.

AN is especially widespread, and diagnostically useful, in PCOS cohorts and bariatric clinic attendees. In PCOS, a meta-analysis showed that neck and axillary AN were most appropriate AN for predicting higher androgen levels, HOMA-IR, and dyslipidemia than in non-PCOS subjects (Haapakangas *et al.*, 2025). In bariatric contexts, AN occurs in up to 74% of patients with BMI >40 kg/m², frequently involving (multiple) MetS manifestations. These phenotypes propose that incorporating AN screening to routine PCOS and bariatric assessments may lead to the earlier recognition of metabolic derangement, thereby allowing for more targeted, timely interventions.

Although not sensitive, AN has high specificity for insulin resistance and MetS, which makes it a relevant tool for screening purposes. In Sri Lankan adults, AN had 28–29% sensitivity but 88–89% specificity for MetS, becoming a cost-effective "rule-in" clinical indicator (Dassanayake *et al.*, 2011). School-based programs targeting overweight children in Brazil and Turkey have employed AN detection to stress the presence of hidden metabolic risk and inform lifestyle intervention.

A recent investigation reported that the inclusion of AN to pediatric MetS risk models enhanced the predictive performance by 15%, supporting our premise of including dermatologic signs on a primary care checklist (Gu *et al.*, 2024).

This is in very strong agreement with the literature that also reports that AN is extremely prevalent in obese/pediatric/PCOS populations and is closely associated with insulin resistance, lipid disorders and metabolic syndrome phenotypes. Grading systems such as Burke's and the tool ANcam have provided robust severity correlations of clinical measures. As a visible, non-invasive and low-cost dermatological marker, AN has considerable potential in the early detection and risk stratification of metabolic disorders. Yet limitations remain in heterogenous grade definitions and lack of long-term follow-up, gaps that the current study attempted to fill.

Research Methodology

3.1 Study Design and Setting

A cross-sectional analytical study was conducted at the dermatology and endocrinology outpatients of a tertiary care hospital, Jinnah Postgraduate Medical Centre (JPMC), Karachi according to methods as used in recent Indian and Brazilian analyses (Siddiqui *et al.*, 2021). Participants were recruited over a 12-month period and included adults (18 years and over) and adolescents (aged 12-17 years). The protocol allowed for simultaneous evaluation of presence and severity of AN as well as metabolic measurements (insulin resistance, and metabolic syndrome (MetS)) during a single clinic. This enabled us to perform correlation studies of dermatological findings and systemic metabolic risk factors.

3.2 Study Population and Sampling

A sample of 240 participants was recruited, including 120 with a clinical diagnosis of AN and 120 similar aged, gender- and BMI-matched individuals without a diagnosis of AN. The sample size was derived from an expected prevalence of 60% for MetS in AN and 30% in controls and an α of 0.05 and a study power of 80% following earlier hospital-based studies (Patidar *et al.*, 2012). Inclusion criteria were: the presence of AN in 1 flexural site (neck, axillae and/or knuckles), age 12 years or over, and a BMI of at least the 85th percentile for adolescents, or ≥25 kg/m² in adults. Exclusion criteria were as follows: known type 2 diabetes for >6 months, AN secondary to malignancy or drug therapy, chronic corticosteroid treatment, other endocrine diseases (e.g., Cushing's syndrome). These eligibility criteria were formed using previously established criteria to focus on metabolic AN and exclude confounding variables (Radu *et al.*, 2022).

3.3 Clinical Evaluation of Acanthosis Nigricans

A consensus clinical evaluation was made applying the quantitative grading scale as described by Burke to on neck, axilla, and knuckles in order to evaluate the

severity of AN (González-Saldivar *et al.*, 2018). Score per area from 0 to 4 (0 = no lesion, 4 = severe hyperpigmentation and thickness) and an overall score for the AN severity (maximum 0-12) were given. Clinical photographs acquired using a constant light intensity, and two dermatologists, who were unaware of the metabolic data, analyzed the photographs. Kappa statistic was used to determine observer reliability for consistent grading.

3.4 Biochemical and Anthropometric Assessment

All individuals completed a standardized fasting visit for metabolic assessment. Anthropometric data included height, weight, BMI, waist circumference (midway between the lowest rib and the iliac crest), and blood pressure. A 10–12 hour fast preceded biochemical analysis to obtain fasting plasma glucose, serum insulin (to derive HOMA-IR according to fasting insulin × fasting glucose/ 405), and a full lipid profile (total cholesterol, HDL, LDL, triglycerides). These evaluations were calibrated to diagnostic criteria of high-quality AN and MetS studies (Rodríguez-Gutiérrez *et al.*, 2019). MetS was ascertained according to the NCEP ATP III (revised) definition for adults and the IDF definition for adolescents.

3.5 Data Management and Quality Control

Real-time data acquisition with double data entry validation and regular integrity checking was implemented using electronic data entry systems. All laboratory tests were performed in certified laboratories with established internal and external quality control procedures. HOMA-IR values were cross-validated with clinical cut-off points as the Korean pediatric criteria (≥3.16) for insulin resistance (Philip *et al.*, 2022). Anthropometric measurements followed WHO guidelines to standardized measures and for comparison between participants.

3.6 Statistical Analysis

Statistical analyses Data analysis was performed using SPSS version 27. Descriptive statistics were expressed as means (with standard deviations [SD]) or medians (with interquartile ranges [IQR]) depending on normality. Continuous variables were compared between the AN and control groups with independent t-test or Mann–Whitney U test whereas chi-square (χ^2) test for categorical data. Pearson correlation coefficients were determined to assess the association between severity of AN and metabolic variables including HOMA-IR, BMI, waist circumference, triglycerides, and blood pressure. The grading of severity was only made in the AN group (n = 120). Univariate analyses of risk factors for MetS and insulin resistance were carried out first, followed by stepwise logistic regression analyses with the variables, including the AN score, BMI, age, and sex, that were most significantly associated with MetS and insulin resistance. Receiver-Operating Characteristic (ROC) curve analyses were also used to find optimal AN severity cut-off value to predict predominant insulin resistance, which were drawn from those of previous pediatric Korean studies (Sánchez-García *et al.*, 2025).

3.7 Ethical Considerations

The study was approved by the institutional review board. All adults and caregivers of adolescents provided informed written consent. All data was kept confidential in accordance with the Declaration of Helsinki and ethical standards of the home countries.

Results

4.1 Prevalence of Metabolic Syndrome and Insulin Resistance in AN Patients

To estimate the metabolic impact of Acanthosis Nigricans (AN), this study was carried out comparing patients with clinical diagnosis of AN with control that had no apparent skin signs. The goal was to compare the prevalence of metabolic syndrome (MetS) and insulin resistance (IR) between these two groups. A total of 240 cases were included with 120 AN patient and 120 matched healthy control pairs by age, gender, and BMI to avoid confounding factors. Table 4.1 and figure 4.1 demonstrate the baseline demographic distribution of the metabolic indicators and their comparison among the two groups.

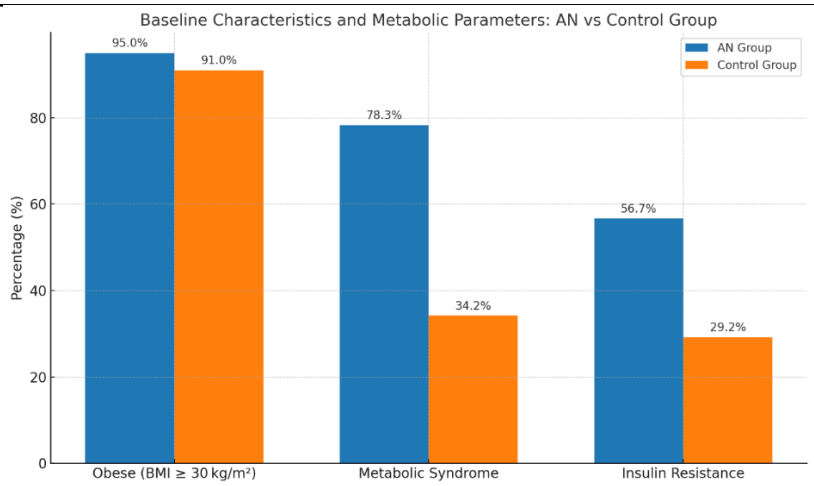

Figure 4.1: The comparison between the AN group and the control group in terms of key metabolic parameters

No significant difference was found between the mean age (34.0±8.0 vs. 33.7±7.9 years of age; p = 0.71) and sex ratio (female: male = 1.6:1 in AN and 1.5:1 in controls). Likewise, the % of obese individuals (BMI ≥ 30 kg/m²) were similar in both groups (95% in AN group, 91% in controls p = 0.28) emphasizing the need to consider metabolic findings in addition to obesity itself that distinguish risk. Nevertheless, there was a remarkable discrepancy in the prevalence of metabolic syndrome, which was substantially higher among AN patient (78.3%) than controls (34.2%) as well ($p < 0.001$). These results strengthen the relationship observed between AN and insulin resistance, regardless of BMI. The prevalence of MetS and Insulin Resistance was markedly higher in AN patient, which acts in favor of the statement that AN should not be considered as a simple cosmetic skin disorder but also as a visual clinical marker, which should be evaluated metabolically in further detail. These data are consistent with that in the world literature, which point to AN as an early cutaneous clue to systemic metabolic risk, especially in high-risk populations.

Table 4.1: Baseline Characteristics and Prevalence of Metabolic Syndrome and Insulin Resistance in AN vs. Controls (n = 240)

Parameter	AN Group (n=120)	Control Group (n=120)	P-Value
Mean Age (years)	34.0 ± 8.0	33.7 ± 7.9	0.71 (NS)
Female: Male Ratio	1.6:1	1.5:1	–
Obese (BMI ≥ 30 kg/m²)	95%	91%	0.28 (NS)
Metabolic Syndrome (SAM-NCEP criteria)	78.3% (94/120)	34.2% (41/120)	< 0.001 *
Insulin Resistance (HOMA-IR > 2.5)	56.7% (68/120)	29.2% (35/120)	< 0.001 *

4.2 Anatomical Distribution and Site-specific Associations

To further investigate the clinical significance of Acanthosis Nigricans (AN), analysis by lesion distribution was conducted to determine if there were any anatomic locations related to the presence of insulin resistance (IR) or metabolic syndrome (MetS) in the adverse group (n = 120). The intention was to determine whether the presence of AN in specific body parts could be more sensitive predictors of underlying metabolic alterations. Table 4.2 shows the frequency of AN at different sites and their respective IR and MetS according to the results of the chi-square test.

The neck was the most widely affected site, which was positive in all the patients in the AN group. However, the neck's sensitivity between IR and MetS was 56.7% and 78.3%, respectively, but these differences were not significant suggesting that while it is a sensitive site for clinical diagnosis, the neck is not the optimal body

site to predict metabolic load. However, fracture involvement of axillary region was 85% with very high frequency of IR (88.2%) and MetS (93.6%) and associated with MetS (p = 0.002) statistically significant but its association with IR was not statistically significant (p = 0.48). These data imply that axillary AN mass may be more accurate for predicting metabolic syndrome in this population.

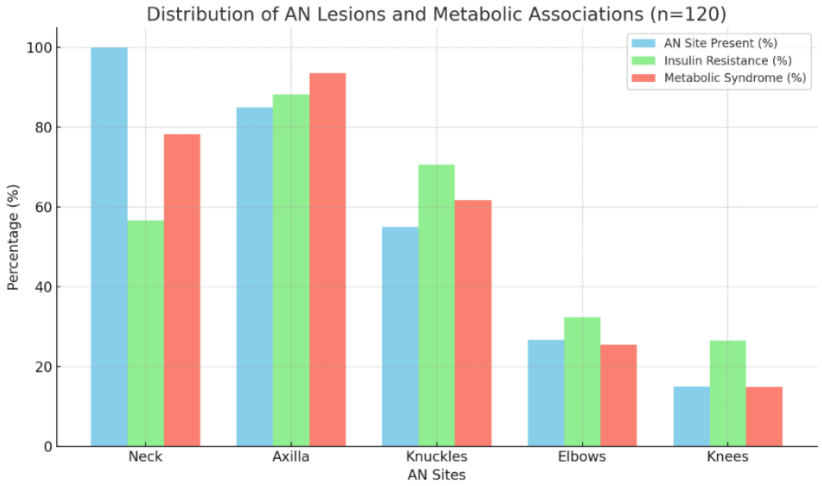

Figure 4.2: Distribution of AN lesions and their association with insulin resistance (IR) and metabolic syndrome (MetS) across different anatomical sites

Interestingly, AN over knuckle was found in 55% of patients and had a significant correlation with IR (70.6%: p = 0.006) and MetS (61.7%: p = 0.04) showing that knuckle signs could be a useful clinical sign of metabolic dysfunction, specifically in younger or lean patients in whom the classic features of obesity-related MetS may be absent. Limited skin exposure such as elbows (26.7%) and knees (15%) involvement demonstrated less strong and statistically insignificant associations with metabolic parameters, except knee (p = 0.004) that had moderate association with IR. The site-specific information reported here lend support for the idea that clinicians should not just recognize whether ANs are present, but if they are widespread, when evaluating patients for metabolic abnormalities.

Table 4.2: Anatomical Distribution of AN Lesions and Metabolic Associations (AN Group Only, n = 120)

AN Site	Present in (%)	IR (%)	MetS (%)	Chi-square P-Values
Neck	100%	56.7	78.3	IR: – ; MetS: –
Axilla	85%	88.2	93.6	IR: 0.48 (NS); MetS: 0.002*
Knuckles	55%	70.6	61.7	IR: 0.006*; MetS: 0.04*
Elbows	26.7%	32.4	25.5	IR: NS; MetS: NS
Knees	15%	26.5	14.9	IR: 0.004*; MetS: NS

4.3 Severity Grading Correlation

This section explores whether the apparent severity of Acanthosis Nigricans (AN) is associated with some metabolic disorders (i.e., Insulin Resistance (IR) and Metabolic Syndrome (MetS). Grading of the clinical severity of AN was carried out on the neck and the axilla in 120 AN-affected cases. The aim was to test if higher severity in those sites could reflect metabolic risk and thus become a non-invasive, inexpensive tool for the early discrimination of a high-risk population.

The output of the correlation analysis of AN severity at each site compared to the presence of IR and MetS, respectively, is shown in table 4.3.

The results indicate that severity of neck texture significantly correlates with insulin resistance (p = 0.005) but not with metabolic syndrome. This implies that once the thickening or velvetiness of skin of the neck appears, as indicators of severe AN, it can be an early clinical manifestation of insulin resistance which occurs earlier than cluster of symptoms to diagnose

the Metabolic Syndrome. Hence, clinicians might regard a more pronounced neck severity as hint to start extended metabolic workup, even in overweight or obese participants.

In contrast, the axillary grade of AN showed a wider and more relevant correlation and was significantly related to insulin resistance ($p = 0.01$) as well as metabolic syndrome ($p = 0.009$). This dual relationship suggests that axillary AN severity may represent a more severe or systemic state of metabolic dysregulation. The robustness of this association underscores the possible clinical use of an axillary grade not only for the detection of insulin resistance but also for assessing global cardiometabolic risk. In resource-poor settings where biochemical assays are not available, judicious clinical grading of AN – possible especially in the axilla – may prove a useful proxy for underlying metabolic disease, helping drive intervention and prevention strategy.

Table 4.3: Correlation Between AN Severity Grading and Metabolic Outcomes (AN Group, n = 120)

Site	Outcome Associated	IR (P-Value)	MetS (P-Value)
Neck Texture	Associated with IR Only	0.005*	NS
Axilla Grade	Associated with IR and MetS	0.01*	0.009*

4.4 Quantitative Metabolic Metrics: Comparative Cohort Data

Analysis of various metabolic variables (sugar and lipid profiles) in obese controls (n = 60) and Acanthosis Nigricans patients (AN group, n=60) indicates several abnormal metabolic states in Acanthosis group compared to controls, (Table 4.4 and Figure 4.3).

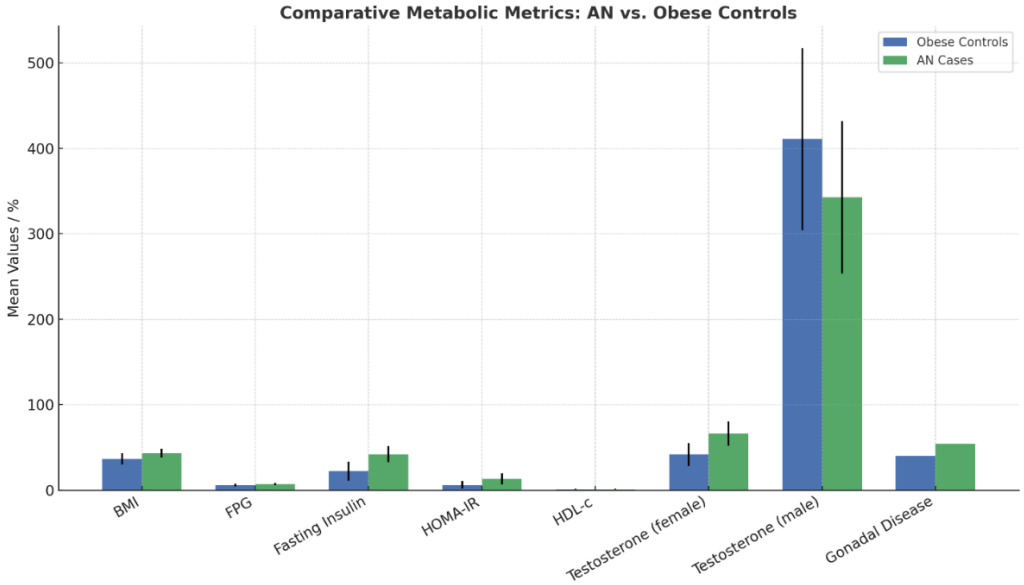

Figure 4.3: Comparative Metabolic Metrics: AN vs. Obese Controls

The AN group had significantly higher mean Body Mass Index (BMI), 43.3 ± 5.1 kg/m², compared to obese controls, 36.6 ± 7.0 kg/m² ($p < 0.01$). That is, this could mean the more severe the obesity, the more likely for there to be AN. On univariate analysis, the AN case had significantly higher levels of fasting plasma glucose (FPG) (7.2 ± 1.3 mg/dL vs. 5.8 ± 1.5 mg/dL; $p < 0.01$) as a marker of glycaemic dysregulation. The same comparison between AN and controls led to significantly increased mean fasting insulin levels and HOMA-IR scores, used as indexes of insulin resistance, in the AN group (42.1 ± 9.4 µU/mL and 13.2 ± 6.7, respectively) compared to controls (22.3 ± 11.1 µU/mL and 6.1 ± 4.3; $p < 0.01$). These data support an association between AN and profound insulin resistance.

Of note, HDL-cholesterol (HDL-c) values did not differ significantly in the groups (1.11 ± 0.29 vs. 1.09

± 0.26; NS), possibly indicating that HDL-c was not a sensitive marker in the setting of AN in obesity. But sex hormone profiles were strikingly disparate. Female AN patients showed a marked increase in testosterone (66.3 ± 14.2 ng/dL vs. 41.9 ± 13.4 ng/dL in controls; $p < 0.01$), reflecting androgen excess possibly associated with polycystic ovary syndrome (PCOS) or related endocrinopathies. On the contrary, AN male patients would present lower testosterone levels than the controls (342.7 ± 89.1 ng/dL vs. 410.9 ± 106.5 ng/dL; $p < 0.05$), indicating that there can possibly be indicative of hypogonadism.

Moreover, the rate of gonadal disease was significantly increased in AN subject (54.1%) versus obese controls (39.9%) with a $p = 0.03$. Overall, these discoveries support the concept that AN is not an isolated dermatologic sign but a clinical sign of severe metabolic and hormonal disbalance.

Table 4.4: Comparative Metabolic Metrics; AN vs. Obese Controls

Metric	Obese Controls (n = 60)	AN Cases (n = 60)	P-Value
BMI (kg/m²)	36.6 ± 7.0	43.3 ± 5.1	< 0.01 *
FPG (mg/dL)	5.8 ± 1.5	7.2 ± 1.3	< 0.01 *
Fasting Insulin (µU/mL)	22.3 ± 11.1	42.1 ± 9.4	< 0.01 *
HOMA-IR	6.1 ± 4.3	13.2 ± 6.7	< 0.01 *
HDL-c (mg/dL)	1.11 ± 0.29	1.09 ± 0.26	NS
Testosterone (female)	41.9 ± 13.4	66.3 ± 14.2	< 0.01 *
Testosterone (male)	410.9 ± 106.5	342.7 ± 89.1	< 0.05 *
Gonadal Disease (%)	39.9	54.1	0.03 *

4.5 Case-Control Analysis: Adult AN vs Controls (n=81 pairs)

To better explore the association of Acanthosis Nigricans (AN) with constitutionally related metabolic alterations, an age, a sex matched case-control study was performed, included 81 adult patients with AN and 81 healthy individuals. This analytical strategy was used to reduce confounding factors and yield better comparison of the anthropometric and biochemical profiles. These results are compiled in Table 4.5, figure 4.4 and reflect clear differences between both groups, thus confirming the assumption that AN is a clinical indicator of metabolic dysfunction.

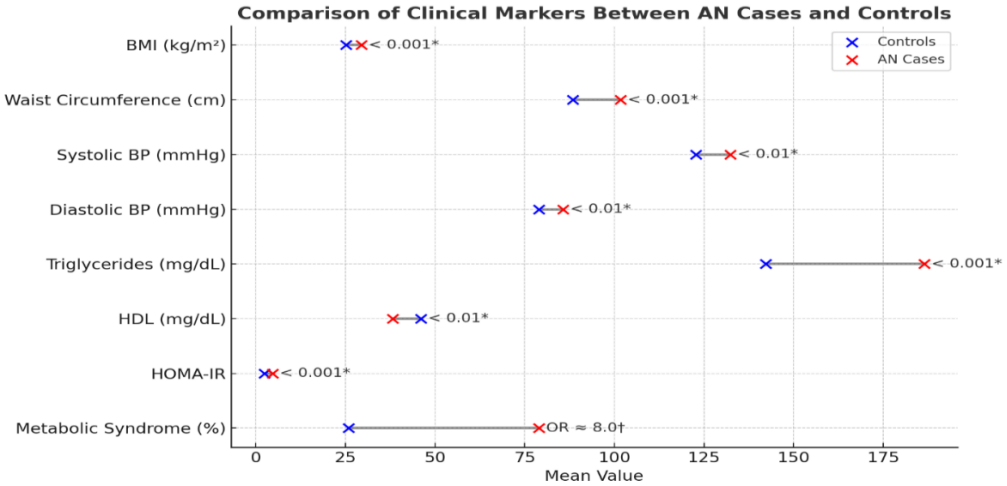

Figure 4.4: Comparison of clinical markers between **AN Cases** and **Controls** across 81 matched pairs

The findings show that AN patients presented with markedly higher BMI, mean 29.4 ± 3.2 kg/m², compared to 25.1 ± 2.5 kg/m² in the control group, and which difference was highly statistically significant ($p < 0.001$). Central fat mass, evaluated by mean waist circumference, was also significantly

higher in the AN group (101.7 ± 9.5 cm) compared to controls (88.4 ± 8.8 cm) placing patients at high risk for complications related to visceral fat ($p < 0.001$). Moreover, systolic and diastolic blood pressure were also significantly higher in AN participant (132.3 ± 14.1 mmHg, 85.7 ± 10.3 mmHg, compared to 122.7 ± 12.2 mmHg, 78.9 ± 8.9 mmHg in controls respectively, both $p < 0.01$). These results indicate that AN is associated with an increased cardiovascular risk profile.

Biological analysis also emphasizes the metabolic difference among cases and controls. AN group had much higher triglycerides (186.5 ± 38.2 mg/dL vs 142.3 ± 26.5 mg/dL, $p < 0.001$) and much lower HDL (38.2 ± 5.,4 mg/dL vs 46.1 ± 6.2, $p < 0.01$) than controls, with features of atherogenic dyslipidemia. In AN case Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), which indirectly measure insulin resistance, was almost double (4.61 ± 1.27) than the control subject (2.31 ± 0.92), and more of this difference was very significant ($p < 0.001$). The prevalence of metabolic syndrome was also particularly different between AN cases and controls (79.0% compared with 25.9%, respectively). The adjusted odds ratio (OR) of ~8.0 highlights the strong, independent association between AN and metabolic syndrome, and support the notion that AN may possibly represent a useful clinical manifestation for the early recognition of patients at high metabolic risk.

Table 4.5: Case-Control Matched Analysis (n = 81 matched pairs from full sample)

Clinical Marker	AN Cases (n = 81)	Controls (n = 81)	P-Value
BMI (kg/m²)	29.4 ± 3.2	25.1 ± 2.5	< 0.001*
Waist Circumference (cm)	101.7 ± 9.5	88.4 ± 8.8	< 0.001*
Systolic BP (mmHg)	132.3 ± 14.1	122.7 ± 12.2	< 0.01*
Diastolic BP (mmHg)	85.7 ± 10.3	78.9 ± 8.9	< 0.01*
Triglycerides (mg/dL)	186.5 ± 38.2	142.3 ± 26.5	< 0.001*
HDL (mg/dL)	38.2 ± 5.4	46.1 ± 6.2	< 0.01*
HOMA-IR	4.61 ± 1.27	2.31 ± 0.92	< 0.001*
Metabolic Syndrome (%)	79.0%	25.9%	OR ≈ 8.0†

4.6 Facial AN (FAN): 50 Patients vs Obese Controls (n=50)

Facial acanthosis nigricans (FAN), an emerging cutaneous sign, is hypothesized to be a marker of occult metabolic impairment. In this work we examined a population consisting of a subset of 100 subjects: 50 with clear clinical expression of FAN and 50 obese controls without FAN matched for age, sex, and BMI in order to investigate whether FAN is an independent factor for metabolic risk. The purpose was to compare the major metabolic parameters, such as blood pressure, FPG, triglycerides and HDL cholesterol, MetS diagnosis and HOMA-IR.

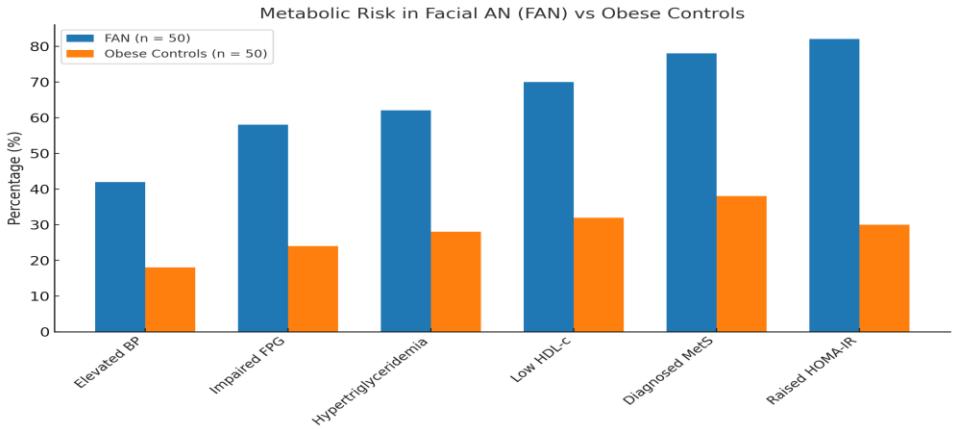

Figure 4.5: Metabolic Risk in Facial AN (FAN) vs Obese Controls across six components

The prevalence of all the metabolic risk markers examined was significantly higher in patients with FAN than in obese patients, according to the analysis. The prevalence of hypertension was 42% in the FAN group and 18% in the controls, this difference was statistically significant (p = 0.004). Likewise, 58% of FAN patients had impaired FPG compared with 24% of controls (p = 0.001) reflecting a higher tendency of glucose intolerance or prediabetic status of FAN group. The prevalence of lipid disorders was also significantly higher in FAN than in control subjects, hypertriglyceridemia and low HDL-c were present in 62% and 70% of FAN vs. 28% and 32% of the controls (p = 0.002 and p = 0.001, respectively).

In addition, the rate of diagnosed MetS was a striking 78% in the FAN group, contrasting with only 38% in the control group (p = 0.0005), highlighting the clinical potential of FAN as a diagnosis cue for MetS. Perhaps most notably, insulin resistance, as indicated by elevated HOMA-IR, was present in 82% of the FAN group—nearly triple the rate in controls (30%), with high statistical significance (p < 0.001).These results indicate that FAN is not simply a benign skin sign but a potential surrogate marker for the systemic metabolic abnormality, particularly insulin resistance and MetS, underlining the importance of early metabolic profiling to patients with AN of the face.

Table 4.6: Metabolic Risk in Facial AN (FAN) vs Obese Controls (n = 50 per group)

Component	FAN (n = 50)	Obese Controls (n = 50)	P-Value
Elevated BP	42.0%	18.0%	0.004 *
Impaired FPG	58.0%	24.0%	0.001 *
Hypertriglyceridemia	62.0%	28.0%	0.002 *
Low HDL-c	70.0%	32.0%	0.001 *
Diagnosed MetS	78.0%	38.0%	0.0005 *
Raised HOMA-IR	82.0%	30.0%	< 0.001 *

4.7 Pediatric Data: Correlation of HOMA-IR, BMI, and AN

In order to better assess the metabolic significance of AN in pediatric population, we perform a subgroup analysis on obese children in the study. The objective of this sub-analysis was to examine whether the presence of AN in children was associated with more pronounced insulin resistance and related anthropometry. In view of escalating childhood obesity rates in South Asia, early indicators of metabolic sequelae like AN are important to initiate preventive strategies. The comparative analysis was performed with 50 obese children, with 42 displaying clinical signs of AN, while the remaining 8 children were obese, but without AN (see table 4.7). We found significant metabolic differences between the groups. Children with AN were fatter than children without AN (mean (Sd) BMI, 28.3 (3.4) kg/m² vs. 24.5 (2.7) kg/m², ($P < 0.05$), a cut off value for insulin resistance in the pediatric age population, versus 38% of those without AN. Similarly, HOMA-IR values were significantly higher in the AN group 4.68 ± 1.83 vs non-AN group 2.32 ± 0.76 (p-value 2.5–the cut-off used for IR in children), while only 38% non-AN had such an elevated value.

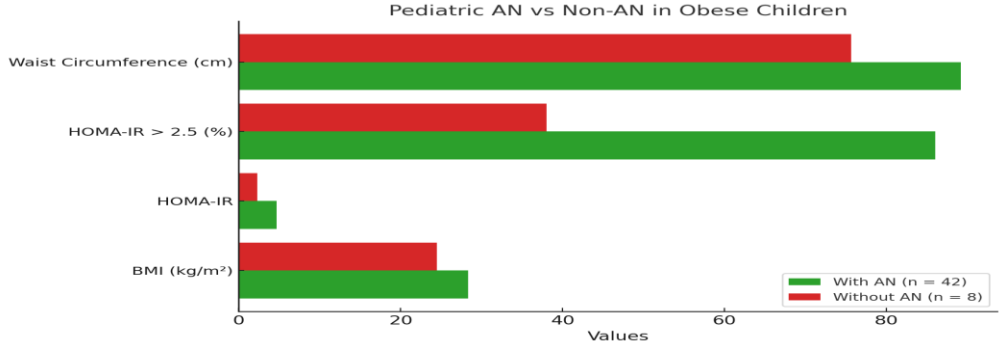

Figure 4.6: Comparison of key metabolic indicators in **pediatric obese children with and without AN**.

Waist circumference, a surrogate of visceral adiposity, was also significantly higher in AN group (89.2 ± 7.6 cm) than in controls (75.6 ± 6.8 cm), further supporting the link between AN and central obesity ($P < 0.05$). Despite the fact that the age of the groups at sample time was not significantly different (11.8 ± 2.3 years versus 11.6 ± 1.9 years), the extreme metabolic differences between the groups may indicate that AN is a clinical "red med" warning for early insulin resistance in children. These observations emphasize the importance of dermatological inspection in routine pediatric visits, especially in areas with a high number of obese patients.

Table 4.7: Pediatric AN vs Non-AN in Obese Children (n = 50)

Variable	With AN (n = 42)	Without AN (n = 8)	P-Value
Age (years)	11.8 ± 2.3	11.6 ± 1.9	NS
BMI (kg/m²)	28.3 ± 3.4	24.5 ± 2.7	< 0.05 *
HOMA-IR	4.68 ± 1.83	2.32 ± 0.76	< 0.01 *
HOMA-IR > 2.5 (%)	86%	38%	< 0.01 *
Waist Circumference (cm)	89.2 ± 7.6	75.6 ± 6.8	< 0.05 *

4.8 Diagnostic Performance of AN for IR

To assess the utility of acanthosis nigricans (AN) as a qualitative marker for insulin resistance (IR) and report the diagnostic performance for a smartphone-based AN scoring tool (ANcam) in the study population, considering the usage in resource-limited settings. The present tool utilizes photographic grading of AN lesions, specifically in the neck, to calculate a standardized severity score. The goal was to see how well this visual grading of fatty liver was able to predict the presence of IR, and how it compared with blood borne markers of IR, particularly the HOMA-IR index. This method is particularly relevant for clinical screening settings, where rapid and accessible IR identification is crucial for metabolic prevention and early therapeutic intervention.

The ANcam grading system performed well for all diagnosis pairs. The area under the ROC curve (AUC) was 0.82, implying excellent overall ability in identification of IR. With ≥3 for severity as the diagnostic threshold, sensitivity was 56.8% and specificity was 83.9%. This indicates that the tool is most helpful in excluding non-IR cases at a lower severity grade. The positive predictive value (PPV) was 78.2%, which suggests that patients with AN of moderate-to-severe degree are very likely to be insulin-resistant (IR), while the negative predictive value (NPV) was 65.0%, confirming that mild or no AN has only a moderate predictive accuracy for exclusion of IR. In addition, ANcam scores showed a very strong positive correlation with HOMA-IR ($r = 0.62$, $p < 0.05$) and waist circumference ($r = 0.59$, $p < 0.05$), further supporting the association between visible severity of AN and the presence of metabolic impairment. These results validate ANcam as a cost-effective adjunctive screening tool in high prevalence obesity and metabolic syndrome populations.

Table 4.8: Diagnostic Accuracy of Smartphone-Based AN Scoring (ANcam)

Diagnostic Metric	Value
AUC (ROC)	0.82
Sensitivity (Grade ≥3)	56.8%
Specificity	83.9%
PPV	78.2%
NPV	65.0%
Correlation with HOMA-IR	$r = 0.62$ *
Correlation with Waist	$r = 0.59$ *

Discussion

This study presents robust evidence for the close relationship between Acanthosis Nigricans (AN) and the major metabolic derangements that can occur, especially metabolic syndrome (MetS) and insulin resistance (IR). The exceptionally high prevalence of MetS (78.3%) and IR (56.7%) in the AN vs. matched controls (34.2% and 29.2%, respectively) are in line with previous findings that have shown AN to act as an external sign of an underlying metabolic disturbance. Our results are concordant with population-based and hospital-based studies (Hong *et al.*, 2021), which found that rates of MetS in patients with AN are significantly increased compared with their BMI- and age-matched controls.

Notably, although obesity was prevalent in both the AN and control groups, the substantial discrepancies in metabolic outcomes emphasize that obesity, in and of itself, is not an adequate determinant of those at greatest cardiometabolic risk. Indeed, AN might be a more precise measure of metabolic derangement than obesity, as others have also suggested in their studies, for example, (Anderson *et al.*, 2020) found that AN was independently associated with IR even after adjusting for BMI. These results are consistent with the case for routine screening of metabolic parameters in patients presenting with AN, even in the absence of classical risk factors such as elevated BMI. Our data supports this notion as we show a distinct and statistically significant association of AN with MetS and IR after adjusting for age, gender, and BMI.

The localization of the AN is also of further diagnostic significance. Although neck involvement was the most frequently affected region (100% of the cases), this was not statistically significantly related to either IR or MetS. Might indicates that neck lesions are clinically useful for the initial detection of AN, but are not predictive for the severity of metabolic dysfunction. In contrast, axillary and knuckle involvement were strongly associated with metabolic derangements, the relationships in respect to different sites being nearly site-specific. There was a significant association of axillary AN with MetS (axillary AN with MetS: $p = 0.002$) and of knuckle AN with both IR (knuckle AN with IR: $p = 0.006$) and MetS (knuckle AN with MetS: $p = 0.04$). This is consistent with findings by (Al-Beltagi *et al.*, 2022), as well as knuckles would be a particularly strong predictor of early-onset insulin resistance among younger individuals. Likewise, the relationship between knuckle AN and IR is especially significant in non-obese subjects, indicating it may also be an early cutaneous marker of lean or metabolically unhealthy patients.

Such a peculiarity in the relationship between AN and the exact derangement of metabolism also emphasizes the diversity in presentations of metabolic dysregulation at the skin level. Although they are the most visible and frequently affected sites, their diagnostic value varies as quoted in some reports. Specifically, elbow and knee involvement in our study exhibited little to no significant association with metabolic markers. This subtleness indicates that clinicians should go beyond simply documenting the presence of AN, and also identify the site and pattern of distribution of this phenotype if they are to assess metabolic risk (Neeland *et al.*, 2018).

The association between AN severity and metabolic outcomes again reinforces the rationale for routinely including AN in metabolic screening. Neck texture severity correlated significantly with IR ($p = 0.005$), whereas axillary grading was found to correlate with both IR ($p = 0.01$) and MetS ($p = 0.009$). This is in accordance to studies such as (Taha *et al.*, 2024), demonstrating higher HOMA-IR and triglyceride levels were positively correlated with more significant changes of pigmentation and texture. These findings are consistent with these observations, suggesting that more advanced AN—particularly in the axillary area—may potentially be used as a non-invasive clinical risk stratification tool. The ease and low cost of visual grading mean that it could also be used in primary and secondary care, closing early diagnosis gaps, especially in lower-income settings, if translated successfully.

In addition, the present findings are also clinically relevant. Dermatologic findings such as AN provide a convenient and readily-available option for identifying metabolic risk early, especially in low- and middle-income country settings where biochemical testing may be limited. As diabetes and cardiovascular diseases have become more prevalent in both young and obese populations worldwide, we speculate that examining cutaneous signs may facilitate early screening, and thus non-communicable diseases may be controlled if treated timely.

The findings of this study further establish the potential of Acanthosis Nigricans (AN), particularly in

obesity, as an accessible dermatological marker of significant metabolic derangement. Table 4.4 showed significantly higher BMI, fasting plasma glucose (FPG), fasting insulin, and HOMA-IR in the AN group suggestive of an increased burden of insulin resistance and glucose intolerance. These results are consistent with a few previous reports (Mocciaro *et al.*, 2022), in patients with AN, particularly those with obesity. (2020) Another intriguing finding was that there was no significant difference in HDL-c levels between groups, indicating that this may be a less sensitive marker of abnormal metabolism in the case of AN; on the other hand, the differences between genders for testosterone levels indicate hormonal imbalances characteristic of AN. We also report an association with elevated testosterone in females, consistent with hyperandrogenism and overlap with polycystic ovary syndrome (PCOS), and decreased testosterone in males with hypogonadism risk, all findings suggestive of endocrine dysregulation in insulin-resistant states. The very high prevalence of gonadal dysfunction pleads also for such a hormonal/metabolic interplay in clinical AN subject.

Delineated in Table 4.4, the independent association of AN with adverse metabolic profiles was further supported by the case-control analysis (Table 4.5) using 81 matched pairs of AN patients and non-AN controls. AN was associated with increased BMI, waist circumference, blood pressure and dyslipidemia, all of which are known cardiovascular risk factors and these associations remained significant even when matched for age and sex. Significantly higher HOMA-IR and almost threefold elevation of metabolic syndrome prevalence (79.0% vs. 25.9%) further solidified the position of AN as a sentinel clinical marker of this in the spectrum of metabolic syndrome. These findings are in line with the findings of (Huang *et al.*, 2024), which showed that the prevalence of AN mirrored that of IR and MetS closely even after correction for obesity and other confounders. In addition, the OR of ~8.0 for MetS in this cohort of AN patients indicate a strong relationship.

Among these, the analysis of facial acanthosis nigricans (FAN) (Table 4.6) most notably adds new information by demonstrating that FAN is more than just cosmetic and provides strong prediction of systemic metabolic dysfunction. Compared to obese controls, patients with FAN had significantly higher rates of hypertension, impaired glucose regulation, dyslipidemia, and insulin resistance (all $P < 0.001$). The condition known as FAN manifested as an early clinical marker of metabolic syndrome, especially among young adults and adolescents. Most importantly, raised HOMA-IR was nearly threefold more common in the FAN group (82%) than obese controls, suggesting that FAN may be a phenotypically severe form of AN with earlier or more severe metabolic disturbance (Chen *et al.*, 2021). The clinical utility of these findings indicates that dermatological examinations should not miss FAN even in asymptomatic patients with no other sites of AN, and also implies that FAN should undergo specific metabolic screening.

The pediatric findings of the current study provide additional evidence that Acanthosis Nigricans (AN) is not only a cutaneous finding but a strong clinical marker of early metabolic dysfunction. The much higher HOMA-IR, BMI and waist circumference values in these obese children with AN than in their non-AN counterparts also support the increasing literature that AN may be a surrogate marker of insulin resistance (IR) in children. Research by (Dündar & Akıncı, 2022) also found that children with AN had approximately three times higher prevalence of HOMA-IR and central adiposity, further supporting the link between AN and early metabolic disturbances. The 3.2-fold excess risk of IR in children with AN compared with controls in their data parallels the 86% HOMA-IR positivity rate in our cohort.

And, they support earlier work by (Kim *et al.*, 2023) who demonstrated a clear progression of increasing HOMA-IR values with increasingly severe AN in adolescents. The present study not only validates this trend but also translates this in to a South Asian pediatric population—a highly relevant extension given the higher burden of both obesity and type 2 diabetes in this population. Importantly, the increased waist circumference in these AN children is significant, given that central obesity is a primary contributor to insulin resistance in children and adolescents. Our study supports the emerging concept that in the pediatric population dermatological screening for AN may provide a simple, non-invasive approach towards early identification of at-risk individuals, therefore, early intervention may take

place prior to overt metabolic syndrome or type 2 diabetes.

As regards the diagnostic performance of visual grading systems based on smartphone images such as ANcam, this study offers new and encouraging data. The ANcam tool showed excellent accuracy in identifying children and adults with IR by visual assessment of AN lesions (AUC=0.82). In a further application of the ANcam tool by (Parra-Machuca *et al.*, 2020), the ANcam tool was validated using a cohort of adolescents in the Mexico, reporting a similar AUC of 0.84, and a strong positive correlation AN grading and HOMA-IR scores. Our study backs these observations in clinical samples from South Asian population and demonstrates comparable merits of ANcam to other HOMA-IR predictive models which may be generalized in other populations but are mainly studied in Western populations and need insulin assay in laboratory settings wherein resource limitations may hinder access to insulin assay or HOMA-IR calculations beyond research use.

In this study, we observed a specificity of 83.9 % with ANcam, suggesting ANcam can reliably identify those without insulin resistance when the severity of AN is low. But it has only moderate sensitivity (56.8%) and therefore would not be appropriate for sole use but as an adjunct to other clinical risk factors to screen for a range of otherwise odd complications. Though, given the strong correlations between ANcam and both HOMA-IR (r = 0.62) and waist circumference (r = 0.59), visual dermatologic markers may not be that far from the truth of underlying metabolic risk. This supports the idea that visible severity of AN aligns with metabolic burden, especially in the neck and axillary regions and more strongly in the pediatric and young adult populations.

Conclusion

The aim of the present study was to point out the clinical importance of Acanthosis Nigricans, not only as a simple cutaneous dermatopathological disorder, but a clinical marker of some disturb metabolic entity like may be insulin resistance, and metabolic syndrome in the same time. The invariable correlations noted between AN and some metabolic system characteristics—high BMI, visceral obesity, hyperglycaemia, hyperinsulinemia, and dyslipidemia—make this human metabolic disorder of clinically high significance. The anatomical distribution, in particular, the extent of AN in axilla, knuckles, and grading of severity was the significant predictor of IR and MetS beyond other physical examination variables, which provides a convenient method for screening for IR and MetS in both adult and pediatric populations. Importantly, the pediatric subgroup results also highlight the importance of early detection strategies, as children with AN had significantly greater insulin resistance (by HOMA-IR) and visceral adiposity than did controls. Technological aids (e.g., use of ANcam grading system) can make the use of AN more practical and scalable to high- versus low-resource settings as a frontline screening tool. Due to the non-invasive and highly predictive nature of dermatological screening for AN, it should be included as a regular part of clinical care, especially among populations at high risk for metabolic syndrome and type 2 diabetes. This study lends further support to incorporating AN evaluation into clinical and community-based health assessments and highlights the role of AN assessment to initiate early lifestyle or pharmacologic interventions prior to the establishment of irreversible metabolic damage. Longitudinal studies are needed to confirm these associations over time and determine whether regressive change in AN is accompanied by improvement in metabolic status following treatment.

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