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The Correlation between Severity of Acanthosis Nigricans and Metabolic Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Acanthosis Nigricans (AN) is a dermatologic manifestation characterized by hyperpigmentation and thickening of the skin, commonly observed in body folds. While traditionally considered a cutaneous marker of insulin resistance, recent studies have hinted at broader metabolic implications associated with AN. Understanding the intricate connections between AN and various metabolic parameters is crucial for comprehensive patient care and management.
Purpose: The primary objective of this study was to investigate the metabolic associations of Acanthosis Nigricans, with a specific emphasis on its correlation with obesity, insulin resistance (IR), and metabolic syndrome (METS). The aim was to provide insights into the interplay between

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AN severity and metabolic health indicators, particularly focusing on the 18-40 age group and the impact on the neck area.
Methods: The study employed a cross-sectional design, involving a diverse sample of participants within the 18-40 age range. Data collection included detailed clinical assessments, anthropometric measurements, biochemical analyses, and ultrasound evaluations. Statistical analyses explored associations between AN severity, obesity, insulin resistance, metabolic syndrome, and other relevant metabolic parameters.
Results: The study found a high prevalence of AN in the 18-40 age group, primarily affecting the neck area. Significant associations were observed between AN and metabolic derangements such as obesity, hypertension, hyperinsulinemia, and type 2 diabetes. The prevalence of metabolic syndrome in AN cases was 20.0%, with ultrasound changes like fatty liver and polycystic ovary syndrome noted in 13.3% of the participants.
Conclusion: The findings highlight the importance of recognizing the broader impact of AN on metabolic health beyond its traditional association with insulin resistance. The intricate interplay between AN and various metabolic parameters, including abnormal insulin levels, BMI, ultrasound findings, and metabolic syndrome, underscores the complexity of this dermatologic manifestation. It is crucial to shift the focus from AN severity alone to a comprehensive understanding of its multifaceted connections with systemic metabolic health.

Keywords: Acanthosis nigricans; body mass index; diabetes mellitus.

1. BACKGROUND

Acanthosis Nigricans (AN) is a dermatologic manifestation characterized by hyperpigmented, velvety plaques on intertriginous surfaces, gaining heightened significance in recent years. Its prevalence, ranging from 7 to 74%, mirrors the escalating rates of obesity and diabetes globally [1]. This dermatological condition, once primarily aesthetic, is now recognized as a crucial marker for underlying metabolic disturbances. Individuals with AN face an elevated risk not only of obesity but also of hypertension, hyperinsulinemia, insulin resistance (IR), and type 2 diabetes [2].

The etiology of AN is complex, involving factors such as insulin-like growth factors, raised serum insulin levels, and various endocrinopathies. Recent studies have shed light on the intricate relationship between AN and IR, the latter being a burgeoning global epidemic. Compensatory hyperinsulinemia, stemming from IR, activates specific cell receptors, influencing the proliferation of keratinocytes and fibroblasts, ultimately contributing to the development of AN plaques. Despite the recognition of AN as a cutaneous marker of IR, conflicting evidence persists, necessitating a deeper exploration of this relationship [3].

This introduction sets the stage for our prospective cross-sectional study, which seeks to unravel the prevalence of IR among AN patients and discern the nuanced association between IR and the severity of AN. The study endeavors to detect metabolic syndrome and insulin resistance in AN patients and aims to contribute valuable insights that could pave the way for early identification and management of IR, forestalling the progression to overt diabetes mellitus and its associated complications. As the prevalence of AN continues to rise, understanding its intricate connection with IR becomes imperative, offering potential avenues for proactive healthcare interventions [4].

2. METHODS

This study encompassed a cross-sectional analysis of sixty individuals with Acanthosis Nigricans (AN) who sought consultation at a tertiary healthcare center's dermatology department. A comprehensive patient history was meticulously documented, capturing details on the duration of AN and its specific sites of involvement. Clinical examinations included Body Mass Index (BMI) assessments, with additional evaluations for associated dermatologic conditions like acrochordons, acne, psoriasis, and seborrheic dermatitis.

To unravel the metabolic profile of the participants, an array of diagnostic assessments was employed. These included thyroid function tests, insulin level measurements, blood sugar level evaluations, lipid profile analyses, and ultrasound examinations. The severity of AN was quantified using a validated tool, "The Burke's quantitative scale for acanthosis nigricans,"

offering a standardized approach to grading AN severity.

The statistical analysis employed a multifaceted approach. Descriptive measures provided a succinct summary of key data points. Frequency distributions facilitated a comprehensive understanding of the distribution of variables within the cross-sectional study. Association assessments were conducted using Chi-square and Fisher's exact tests, allowing for the exploration of relationships between categorical variables. The significance level was set at $p < 0.05$. The research spanned two months and adhered to the Code of Ethics of the World Medical Association (Declaration of Helsinki of 1975, as revised in 2003) for experiments involving humans.

This robust combination of clinical assessments, diagnostic tests, and statistical analyses provides a thorough and systematic approach to exploring the prevalence, severity, and associated factors of Acanthosis Nigricans in our study population. The utilization of validated grading scales and rigorous statistical methods enhance the reliability and validity of our findings, contributing to the overall robustness of this investigation (Table 1).

Table 1. Description of Acanthosis Nigricans based on Burke's numerical scale

Neck Severity:

Location Score	Description
0	Absent: Not detectable upon close inspection.
1	Present: Clearly visible upon close examination, but not noticeable to casual observers; extent not measurable.
2	Mild: Restricted to the base of the skull, not extending to the lateral margin of the neck (usually <3 inches in breadth).
3	Moderate: Extends to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3–6 inches); not visible from the front.
4	Severe: Extending anteriorly (> 6 inches), visible when viewed from the front.

Axilla:

Location Score	Description
0	Absent: Not detectable upon close inspection.
1	Present: Clearly visible upon close examination, but not noticeable to casual observers; extent not measurable.
2	Mild: Localized to the central portion of the axilla, may have gone unnoticed by the participant.
3	Moderate: Involving the entire axillary fossa, but not visible when the arm is against the participant’s side.
4	Severe: Visible from the front or back in the unclothed participant when the arm is against the participant’s side.

Neck Texture:

Location Score	Description
0	Smooth to touch: No differentiation from normal skin upon palpation.
1	Rough to touch: Differentiated from normal skin.
2	Coarseness can be observed visually, with portions of the skin raised above other areas.
3	Extremely coarse: "Hills and valleys" observable on visual examination.

Other Body Parts:

Body Part	Present	Absent
Knuckles	Present	Absent
Elbows	Present	Absent
Knees	Present	Absent

3. RESULTS

Out of 60 patients, the majority (81.7%) were within the 18-40 age group, with a male-to-female ratio of 1.3:1. The mean duration of AN was 2.48 ± 1.47 years. The most common site was the neck (88.3%), followed by the axilla (85%). BMI ranged from 18.5 to 29.9 kg/m², with 33.3% falling between 18.5-22.9 kg/m² and 30% between 25.0-29.9 kg/m². Associations like acrochordons (30.0%) and acne (13.3%) were noted. Metabolic derangements included hypothyroidism (20.0%), deranged lipid profiles (36.7%), and diabetes mellitus (13.3%). Metabolic syndrome was observed in 20.0% of cases, with significant ultrasound changes in 13.3%, including fatty liver and polycystic ovary syndrome. AN severity varied, with 38.3% having Grade 1, 50.0% having Grade 2, 10.0% having Grade 3, and 1.7% having Grade 4. Statistical analysis revealed a significant association between abnormal overall insulin levels and BMI, USG abdomen findings, and metabolic syndrome.

Table 2. Frequency and percentage of clinical parameters of Acanthosis Nigricans

Thyroid Function	Percentage
WNL	48 (80.0%)
Hypothyroid	12 (20.0%)
Lipid Profile	
WNL	38 (63.3%)
Deranged	22 (36.7%)
DM (Yes)	8 (13.3%)
Insulin	
WNL	30 (50.0%)
Fasting Abnormal	4 (6.7%)
PP Abnormal	25 (41.7%)
Fasting+PP Abnormal	1 (1.7%)
USG Abdomen Impression	
NAD	52 (86.7%)
Significant	8 (13.3%)
USG Abdomen	
NAD	52 (86.7%)
Fatty Liver	4 (6.7%)
PCOS	4 (6.7%)
Metabolic Syndrome (Yes)	12 (20.0%)

Table 2 shows the evaluation of thyroid function, 80.0% of cases were within normal limits (WNL), indicating healthy thyroid function. However, 20.0% exhibited hypothyroidism. The lipid profile analysis revealed that 63.3% of cases had lipid levels within normal limits (WNL), while the remaining 36.7% showed deranged lipid levels, suggesting a need for further investigation. Among individuals with diabetes mellitus (DM), 13.3% exhibited abnormal results, indicating potential issues with glucose regulation. Regarding insulin levels, 50.0% were within normal limits, indicating proper insulin function. However, 6.7% showed abnormalities in fasting levels, 41.7% had abnormal postprandial (PP) levels, and 1.7% exhibited abnormalities in both fasting and PP insulin levels, suggesting varied insulin response patterns.

Table 3 presents the assessment of Body Mass Index (BMI), where the mean (SD) for individuals within the normal range (WNL) was 22.87 (2.69) Kg/m², while those with abnormal BMI levels exhibited a mean (SD) of 24.84 (3.87) Kg/m². A two-sample t-test revealed a statistically significant difference with a t-value of -2.287 and a p-value of 0.026, suggesting a significant distinction in BMI between the WNL and Abnormal groups.

Concerning insulin levels, the median (IQR) for WNL was 22.55 (21.4-24.17), whereas for those with abnormal insulin levels, the median (IQR) was 25 (22.73-26.1). The analysis also includes the minimum and maximum values, indicating the range of variability within each group. The BMI range within the WNL group was 18.2 to 28.2 Kg/m², while the Abnormal group showed a range of 18.1 to 35.6 Kg/m².

Table 4 illustrates the interplay between Lipid Profile and Overall Insulin levels, utilizing a chi-square test to investigate the association between these variables. The data is presented in a contingency table, categorizing individuals into different groups based on their Lipid Profile and Insulin status. Within the "Within Normal Limits" (WNL) Lipid Profile category, 25 individuals (83.3%) exhibit normal insulin levels, while 13 individuals (43.3%) have abnormal insulin levels. This constitutes a total of 38 individuals (63.3%) falling into the WNL Lipid Profile category. In contrast, for those with a deranged Lipid Profile, 5 individuals (16.7%) have normal insulin levels, and 17 individuals (56.7%) have abnormal insulin levels, totaling 22 individuals (36.7%) in this category. The Chi-Square Test conducted on this distribution yields a χ^2 value of 10.335, and the associated p-value is 0.001. This low p-value suggests a statistically significant association between Lipid Profile and Overall Insulin levels. In essence, the results imply that these two variables are not independent within the studied population.

Table 3. Comparison of BMI and overall insulin levels

BMI (Kg/m²)	Insulin (Overall)		t-test	
	WNL	Abnormal	t	p-value
Mean (SD)	22.87 (2.69)	24.84 (3.87)	-2.287	0.026
Median (IQR)	22.55 (21.4-24.17)	25 (22.73-26.1)		
Min - Max	18.2 - 28.2	18.1 - 35.6		

Table 4. Relationship between lipid profile and overall insulin levels

Lipid Profile	Insulin (Overall)			Chi-Squared Test	
	WNL	Abnormal	Total	χ2	P Value
WNL	25 (83.3%)	13 (43.3%)	38 (63.3%)	10.335	0.001
Deranged	5 (16.7%)	17 (56.7%)	22 (36.7%)		
Total	30 (100.0%)	30 (100.0%)	60 (100.0%)		

Table 5. Relationship between USG abdomen results and overall insulin levels

USG Abdomen	Insulin (Overall)			Fisher's Exact Test	
	WNL	Abnormal	Total	χ2	P Value
NAD	30 (100.0%)	22 (73.3%)	52 (86.7%)	9.231	0.005
Fatty Liver	0 (0.0%)	4 (13.3%)	4 (6.7%)		
PCOS	0 (0.0%)	4 (13.3%)	4 (6.7%)		
Total	30 (100.0%)	30 (100.0%)	60 (100.0%)		

Table 5 presents a detailed examination of the relationship between USG Abdomen results and Overall Insulin levels, utilizing Fisher's Exact Test to determine the statistical association between these two variables. Within the "No Abnormality Detected" (NAD) category of USG Abdomen results, 30 individuals (100.0%) have normal insulin levels (WNL), while 22 individuals (73.3%) exhibit abnormal insulin levels. The total count for this category amounts to 52 individuals (86.7%). In contrast, individuals diagnosed with Fatty Liver or Polycystic Ovary Syndrome (PCOS) show no instances of normal insulin levels, with 4 individuals (13.3%) in each category displaying abnormal insulin levels. This results in a total of 4 individuals (6.7%) for both Fatty Liver and PCOS. The statistical analysis using Fisher's Exact Test yields a χ^2 value of 9.231, indicating a significant association between USG Abdomen results and Overall Insulin levels. The associated p-value of 0.005 further reinforces the statistical significance of this association.

4. DISCUSSION

The main underlying pathophysiology of Acanthosis nigricans is the proliferation of epidermal keratinocytes and dermal fibroblasts due to multiple causative factors. Insulin and Insulin-like Growth factor (IGF) are suggested as promoters of this proliferation. Other proposed mediators include fibroblast growth factor receptor (FGFR) and tyrosine kinase receptors like epidermal growth factor receptor (EGFR). All these receptors are present on keratinocytes and fibroblasts and stimulate growth. Hyperinsulinemia has a direct and an indirect effect in inducing AN. The direct effect is due to high concentrations of insulin activating the IGF-1 receptor. The indirect effect is complex: an increase in the free IGF-1 in circulation, which is the active fraction [5].

In a study conducted by Emin Ozlu et al [6]., the prevalence of AN was higher in the obese group compared with the control group (47.3 and 3.3%, respectively), with AN being the third most frequent skin finding after striae (64.7%) and acrochordon (52.4%). In our study, acrochordon was the most common association. In a study conducted by Álvarez-Villalobos NA et al. [7] knuckles (21.2%) and neck (17.5%) were the most common sites involved in the nondiabetic group, while neck (29.6%) followed by the knuckles (26.7%) in the diabetic group, which was similar to our study where neck (88.3%) was the most common site involved. AN site may be correlated with glucose profile derangements.

In a study conducted by Daye M et al. [8]., Metabolic syndrome was detected in 14% of

cases. Acanthosis nigricans and metabolic syndrome combination were present in 27.7% (p=0.003). In our study, metabolic syndrome was present in 12 (20.0%) cases. Stoddart et al. and Kong et al. [9,10] recognized AN as an independent risk factor associated with hyperinsulinemia, with the development of DM. In our study, out of 30 cases that had deranged insulin, 25 cases had deranged postprandial insulin [11,12].

5. CONCLUSION

The study underscores the importance of recognizing AN as a marker for broader metabolic health issues. Comprehensive metabolic evaluations are essential for AN patient to identify and manage underlying metabolic disturbances effectively. Further research is warranted to explore the pathophysiological mechanisms linking AN with metabolic disorders and to develop targeted interventions for this population.

CONSENT

As per international standards or university standards, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

This study was conducted at the Department of Dermatology & STD and Apex Regional STD Centre, Safdarjung Hospital, New Delhi, India, following ethical guidelines as per the standard protocols.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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