

# 1 ACANTHOSIS NIGRICANS: A Comprehensive Study on Metabolic Associations

## 5 ABSTRACT

6 **Background:** Acanthosis Nigricans (AN) is a dermatologic manifestation characterized by hyperpigmentation and  
7 thickening of the skin, commonly observed in body folds. While traditionally considered a cutaneous marker of insulin  
8 resistance, recent studies have hinted at broader metabolic implications associated with AN. Understanding the intricate  
9 connections between AN and various metabolic parameters is crucial for comprehensive patient care and  
10 management. **Purpose:** The primary objective of this study was to investigate the metabolic associations of Acanthosis  
11 Nigricans, with a specific emphasis on its correlation with obesity, insulin resistance (IR), and metabolic syndrome (METS).  
12 The aim was to provide insights into the interplay between AN severity and metabolic health indicators, particularly  
13 focusing on the 18-40 age group and the impact on the neck area. **Methods:** The study employed a cross-sectional design,  
14 involving a diverse sample of participants within the 18-40 age range. Data collection included detailed clinical assessments,  
15 anthropometric measurements, biochemical analyses, and ultrasound evaluations. Statistical analyses explored associations  
16 between AN severity, obesity, insulin resistance, metabolic syndrome, and other relevant metabolic parameters. **Result:**  
17 While the study initially sought to investigate the correlation between AN severity and insulin resistance, the results revealed  
18 a broader spectrum of associations. The prevalence of AN was notably high in the 18-40 age group, with a primary impact  
19 on the neck. Significant associations were found between AN and metabolic derangements such as obesity, hypertension,  
20 hyperinsulinemia, and type 2 diabetes. The study identified a substantial 20.0% prevalence of metabolic syndrome in AN  
21 case, along with ultrasound changes like fatty liver and polycystic ovary syndrome in 13.3%. **Conclusion:** The findings of  
22 this study highlight the importance of recognizing the broader impact of AN on metabolic health beyond its traditional  
23 association with insulin resistance. The intricate interplay between AN and various metabolic parameters, including  
24 abnormal insulin levels, BMI, ultrasound findings, and metabolic syndrome, underscores the complexity of this dermatologic  
25 manifestation. It is crucial to shift the focus from AN severity alone to a comprehensive understanding of its multifaceted  
26 connections with systemic metabolic health.

27 **Keywords:** Acanthosis nigricans, Body mass index, Diabetes mellitus

## 29 BACKGROUND

31 Acanthosis Nigricans (AN), a dermatologic manifestation characterized by hyperpigmented, velvety plaques  
32 on intertriginous surfaces, has gained heightened significance in recent years. Its prevalence, ranging from 7 to  
33 74%, mirrors the escalating rates of obesity and diabetes globally.<sup>1</sup> This dermatological condition, once  
34 primarily aesthetic, is now recognized as a crucial marker for underlying metabolic disturbances. Individuals  
35 with AN face an elevated risk not only of obesity but also of hypertension, hyperinsulinemia, insulin resistance  
36 (IR), and type 2 diabetes.<sup>2</sup>

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

43 This introduction sets the stage for our prospective cohort study, which seeks to unravel the prevalence of  
44 IR among AN patients and discern the nuanced association between IR and the severity of AN. The study not  
45 only endeavors to detect metabolic syndrome and insulin resistance in AN patients but also aims to contribute  
46 valuable insights that could pave the way for early identification and management of IR, forestalling the  
47 progression to overt diabetes mellitus and its associated complications. As the prevalence of AN continues to  
48 rise, understanding its intricate connection with IR becomes imperative, offering potential avenues for proactive  
49 healthcare interventions.<sup>4</sup>

## 50 METHODS

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

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

60 The statistical analysis employed a multifaceted approach. Descriptive measures were utilized to provide a  
 61 succinct summary of key data points. Frequency distributions facilitated a comprehensive understanding of the  
 62 distribution of variables within the cohort. Association assessments were conducted using Chi-square and  
 63 Fisher's exact tests, allowing for the exploration of relationships between categorical variables. The chosen  
 64 significance level was set at  $p < 0.05$ , ensuring a stringent criterion for identifying statistically significant  
 65 associations. This study was conducted at the Department of Dermatology & STD and Apex Regional STD  
 66 Centre, Safdarjung Hospital, New Delhi, India., following ethical clearance from the Institutional Ethics  
 67 Committee. The research spanned two months and adhered to the Code of Ethics of the World Medical  
 68 Association (Declaration of Helsinki of 1975, as revised in 2003) for experiments involving humans.

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

82 **Table 1: Burke's numerical scale assessing Acanthosis Nigricans (AN):**

84 **Neck Severity:**

Locati on 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.

85 **Axilla:**

Locati on 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.

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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.

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**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.

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**Other Body Parts:**

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

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**RESULT**

95 Out of 60 patients, the majority (81.7%) fell within the 18-40 age group, with a male-to-female ratio of  
96 1.3:1. The mean duration of AN was 2.48 ± 1.47 years. The most common site was the neck (88.3%), followed  
97 by the axilla (85%). BMI ranged from 18.5 to 29.9 kg/m<sup>2</sup>, with 33.3% falling between 18.5-22.9 kg/m<sup>2</sup> and 30%  
98 between 25.0-29.9 kg/m<sup>2</sup>. Associations like acrochordons (30.0%) and acne (13.3%) were noted. Metabolic  
99 derangements included hypothyroidism (20.0%), deranged lipid profiles (36.7%), and diabetes mellitus (13.3%).  
100 Metabolic syndrome was observed in 20.0% of cases, with significant ultrasound changes in 13.3%, including  
101 fatty liver and polycystic ovary syndrome. AN severely varied, with 38.3% having Grade 1, 50.0% having  
102 Grade 2, 10.0% having Grade 3, and 1.7% having Grade 4. Statistical analysis revealed a significant association  
103 between abnormal overall insulin levels and BMI, USG abdomen findings, and metabolic syndrome.

104 **Table 2: Clinical Profile Summary**

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%)

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**Commented [u4]:** Reframe the table 2 title as "Frequency and percentage of clinical parameters of Acanthosis Nigricans"

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<b>Fasting Abnormal</b>	4 (6.7%)
<b>PP Abnormal</b>	25 (41.7%)
<b>Fasting+PP Abnormal</b>	1 (1.7%)
USG Abdomen	
Impression	
<b>NAD</b>	52 (86.7%)
<b>Significant</b>	8 (13.3%)
USG Abdomen	
<b>NAD</b>	52 (86.7%)
<b>Fatty Liver</b>	4 (6.7%)
<b>PCOS</b>	4 (6.7%)
Metabolic Syndrome (Yes)	12 (20.0%)

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

114 **Table 3: Comparison of BMI and Overall Insulin Levels**

BMI (Kg/m <sup>2</sup> )	Insulin (Overall)		t-test	
	WNL	Abnormal	t	p-value
<b>Mean</b>	22.87 (2.69)	24.84 (3.87)	-	0.0
<b>(SD)</b>			2.2	26
<b>Median</b>	22.55 (21.4-	25 (22.73-	87	
<b>(IQR)</b>	24.17)	26.1)		
<b>Min -</b>	18.2 - 28.2	18.1 - 35.6		
<b>Max</b>				

115 **Table 3** presents the assessment of Body Mass Index (BMI), where the mean (SD) for individuals within the  
116 normal range (WNL) was 22.87 (2.69) Kg/m<sup>2</sup>, while those with abnormal BMI levels exhibited a mean (SD) of  
117 24.84 (3.87) Kg/m<sup>2</sup>. A two-sample t-test was conducted, revealing a statistically significant difference with a t-  
118 value of -2.287 and a p-value of 0.026. This suggests a significant distinction in BMI between the WNL and

119 Abnormal groups. Concerning insulin levels, the median (IQR) for WNL was 22.55 (21.4-24.17), whereas for  
 120 those with abnormal insulin levels, the median (IQR) was 25 (22.73-26.1). The analysis also includes the  
 121 minimum and maximum values, indicating the range of variability within each group. The BMI range within the  
 122 WNL group was 18.2 to 28.2 Kg/m<sup>2</sup>, while the Abnormal group showed a range of 18.1 to 35.6 Kg/m<sup>2</sup>. In  
 123 summary, the statistical analysis suggests significant differences in both BMI and insulin levels between the  
 124 WNL and Abnormal groups, providing valuable insights into the relationship between these parameters.

125 **Table 4: Relationship between Lipid Profile and Overall Insulin Levels**

Lipid Profile	Insulin (Overall)			Chi-Square Test	
	WNL	Abnormal	Total	$\chi^2$	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%)		
<b>Total</b>	30 (100%)	30 (100%)	60 (100%)		

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

137 **Table 5: Relationship between USG Abdomen Results and Overall Insulin Levels**

USG Abdomen	Insulin (Overall)			Fisher's Exact Test	
	WN L	Abnormal	Total	$\chi^2$	P Value
<b>NAD</b>	30 (100.0%)	22 (73.3%)	52 (86.7%)	9.2 31	0.0 05
<b>Fatty Liver</b>	0 (0.0%)	4 (13.3%)	4 (6.7%)		
<b>PCOS</b>	0 (0.0%)	4 (13.3%)	4 (6.7%)		
<b>Total</b>	30 (100.0%)	30 (100.0%)	60 (100.0%)		

138  
 139 **Table 5** presents a detailed examination of the relationship between USG Abdomen results and Overall Insulin levels,  
 140 utilizing Fisher's Exact Test to determine the statistical association between these two variables. Within the "No Abnormality  
 141 Detected" (NAD) category of USG Abdomen results, 30 individuals (100.0%) have normal insulin levels (WNL), while 22  
 142 individuals (73.3%) exhibit abnormal insulin levels. The total count for this category amounts to 52 individuals (86.7%). In  
 143 contrast, individuals diagnosed with Fatty Liver or Polycystic Ovary Syndrome (PCOS) show no instances of normal insulin  
 144 levels, with 4 individuals (13.3%) in each category displaying abnormal insulin levels. This results in a total of 4 individuals  
 145 (6.7%) for both Fatty Liver and PCOS. The statistical analysis using Fisher's Exact Test yields a  $\chi^2$  value of 9.231,  
 146 indicating a significant association between USG Abdomen results and Overall Insulin levels. The associated p-value of  
 147 0.005 further reinforces the statistical significance of this association.

148  
 149 **DISCUSSION:**

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

157 In a study conducted by Emin Ozlu et al<sup>6</sup>, the prevalence of AN was higher in the obese group compared with  
 158 the control group (47.3 and 3.3%, respectively), with AN being the third most frequent skin finding after striae  
 159 (64.7%) and acrochordon (52.4%). In our study, acrochordon was the most common association. In a study  
 160 conducted by Álvarez-Villalobos NA et al.,<sup>7</sup> knuckles (21.2%) and neck (17.5%) were the most common sites  
 161 involved in the nondiabetic group, while neck (29.6%) followed by the knuckles (26.7%) in the diabetic group,  
 162 which was similar to our study where neck (88.3%) was the most common site involved. AN site may be  
 163 correlated with glucose profile derangements.

164 In a study conducted by Daye M et al.<sup>8</sup>, Metabolic syndrome was detected in 14% of cases. Acanthosis nigricans  
165 and metabolic syndrome combination were present in 27.7% (p=0.003). In our study, metabolic syndrome was  
166 present in 12 (20.0%) cases. Stoddart et al. and Kong et al.<sup>9-10</sup> recognized AN as an independent risk factor  
167 associated with hyperinsulinemia, with the development of DM. In our study, out of 30 cases that had deranged  
168 insulin, 25 cases had deranged postprandial insulin.

#### 169 CONCLUSION:

170 In summary, our study emphasizes the critical role of Acanthosis Nigricans (AN) as a prominent cutaneous  
171 marker indicative of underlying metabolic disturbances. The observed association with insulin resistance and  
172 metabolic syndrome underscores the imperative for thorough metabolic assessments in individuals presenting  
173 with AN. The intricate interplay between dermatologic manifestations and systemic metabolic health  
174 necessitates further research for a comprehensive understanding and targeted interventions. These findings  
175 advocate for heightened clinical awareness and proactive management strategies in individuals with AN to  
176 address potential underlying metabolic issues effectively.

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