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ASSOCIATION OF ACANTHOSIS NIGRICAN AND DIABETES MELLITUS TYPE 2- A CASE-CONTROL STUDY.

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Abstract: ***Introduction:*** Acanthosis Nigricans (AN), a dermatological condition characterized by hyperpigmented and velvety plaques, has been increasingly reported as a clinical marker of insulin resistance. However, its association with T2DM and related metabolic parameters needs further exploration. ***Objective:*** To determine the association between AN and T2DM and to assess differences in anthropometric and biochemical parameters. ***Methodology:*** A case–control study was conducted at THQ Hospital Chakesar, Shangla, KPK & Naseem Medicare Bhera, District Sargodha over three months. A total of 200 participants were recruited (100 T2DM cases and 100 controls). Data were collected on demographic characteristics, frequency of AN, obesity (BMI ≥28 kg/m²), RBS, HbA1c, and anthropometric measurements. ***Results:*** The mean age of participants was 46.0 ± 9.0 years. AN was more prevalent in diabetic cases (25%) than controls (4%) ($p<0.001$). Participants with AN had significantly higher BMI (29.6 ± 3.4 kg/m²), waist circumference (102.5 ± 8.6 cm), RBS (186.4 ± 45.8 mg/dl), and HbA1c (7.9 ± 1.1%) compared to those without AN ($p<0.001$). Obesity was present in 72.4% of AN-positive participants versus 29.2% of AN-negative ($p<0.001$). Age ≥40 years was also linked with higher AN prevalence (69% vs. 31%, $p=0.03$), but no gender difference was observed. ***Conclusion:*** AN showed a significant association with obesity, older age, and poor glycemic indicators in T2DM. While these findings highlight the potential of AN as a simple clinical marker for identifying individuals at elevated metabolic risk in resource-limited settings.

Keywords: Acanthosis Nigricans; Type 2 Diabetes Mellitus; Obesity; Waist Circumference; BMI; Insulin Resistance.

INTRODUCTION

World-widely, diabetes mellitus type 2 is one of the most common public health issues, and its incidence is rising, especially in low- and middle-income countries[1]. As type 2 diabetes is associated with multiple complications, it can have a profound impact on affected individuals with serious consequences for society as a whole. Previously, diabetes mellitus was considered a disease of urban populations; however, with increasing urbanization, changing nutritional habits, and sedentary lifestyles, its burden is now extending to middle- and low-income populations, including Pakistan[2],[3].

The clinical features of Acanthosis Nigricans (AN) include symmetrically distributed hyperpigmentation and velvety thickening of the skin, particularly over flexural areas such as the nape of the neck and axillae[4]. Although its exact pathophysiology is not fully understood, the most probable mechanisms include the overexpression of local growth factors in the skin and hyperactivity of insulin or insulin-like growth factor-1 (IGF-1) receptors on epidermal cells and melanocytes[5],[6]. AN is not a disease in itself but a cutaneous marker of underlying metabolic or endocrine abnormalities, especially insulin resistance and type 2 diabetes mellitus[7]. Diagnosis is primarily clinical and may be confirmed through skin biopsy when necessary. The condition itself is not directly treatable; instead, management focuses on identifying and addressing the underlying systemic cause[8].

Grandhe et al. conducted a case-control study in the Indian population and reported a higher frequency of AN among diabetic patients (60%) compared to non-diabetic controls (40%)[9]. Another retrospective study conducted in the United States demonstrated that AN can serve as a reliable marker for insulin resistance in type 2 diabetes, while Hoffmann et al. reported a similar association among South African women, linking AN with type 2 diabetes, elevated blood glucose levels, and obesity[10].

The prevalence, presentation, and association of AN vary across ethnicities and geographic regions, influenced by genetic, environmental, and lifestyle factors. To our knowledge, no study has yet been conducted in Pakistan to evaluate the association between AN and diabetes types. Given the country's diverse genetic background, unique dietary patterns, and varying lifestyle practices, findings from other populations may not accurately represent local trends. Establishing this association in our population will help clinicians identify individuals at risk of type 2 diabetes through a simple, non-invasive examination.

Therefore, this study aims to determine the association between Acanthosis Nigricans and Type 2 Diabetes Mellitus and to evaluate differences in metabolic and anthropometric parameters between individuals with and without AN. By addressing these objectives, the study seeks to clarify the strength of this association and the extent to which metabolic risk factors differ between affected and non-affected individuals.

METHODOLOGY

This was a case–control study conducted at THQ Hospital Chakesar Shangla, KPK & Naseem Medicare Bhera, District Sargodha from 26th September 2024 to 26 January 2025. The design was chosen because Acanthosis Nigricans (AN) is relatively uncommon and this approach allowed direct focus on affected individuals. The study was approved by the Institutional Review Board of College of Family Medicine, Pakistan (Ref. No. IRB/CFMP/14/2024/), and written informed consent was obtained from all participants. The cases comprised patients already diagnosed with Type 2 diabetes mellitus, while the controls were apparently healthy, non-diabetic subjects.

All participants were aged 18 years or older to ensure inclusion of only Type 2 diabetes cases and were permanent residents of District Shangla. Individuals taking medications known to induce AN were excluded. Those with other endocrine or systemic conditions known to cause AN were also excluded based on history, examination, and relevant laboratory investigations suggested by a medical consultant. The calculated sample size was 200 participants (100 cases and 100 controls) using OPENEPI, assuming a 40% prevalence of AN among controls9 and 60% among cases, at a 95% confidence level and 80% power. Institutional approval was obtained from the hospital in-charge and the District Health Officer.

Acanthosis Nigricans was diagnosed clinically based on the presence of velvety, hyperpigmented, thickened plaques on the posterior neck and axillae, following the diagnostic criteria described by Hoffmann et al., and confirmed by a medical consultant.4 All eligible subjects were invited to participate, the study objectives and procedures were explained, written informed consent was obtained, and confidentiality was ensured. Detailed history and clinical examination were conducted under supervision of a medical consultant. Type 2 diabetes was diagnosed using the American Diabetes Association criteria: 2-hour OGTT plasma glucose ≥200 mg/dl, fasting plasma glucose ≥126 mg/dl, or HbA1C ≥6.5%.

Data were recorded on a structured proforma, including demographic variables (age, gender), presence of AN, and BMI cutoff of >28 kg/m² was used to define obesity according to the Asia-Pacific classification by the World Health Organization Expert Consultation (2004), which recommends lower thresholds for overweight and obesity in Asian populations due to a higher risk of metabolic disorders at comparatively lower BMI levels.16 Moreover, RBS, HbA1C, waist circumference, height, and weight. The primary outcome was the association between AN and Type 2 diabetes, and the secondary outcome was the difference in BMI, RBS, HbA1C, waist circumference, and obesity between individuals with and without AN.

All personal identifiers were replaced with study codes and stored securely; electronic data were password protected and encrypted, while physical files were kept in locked cabinets. Only essential research team members accessed raw data, and any shared datasets were fully de-identified. Participants were informed about data use and storage at the time of consent. Data analysis was performed in SPSS version 20. Percentages and frequencies were computed for all categorical variables such as gender, obesity, and presence of AN in both groups. Mean and standard deviation were calculated for quantitative data including age, HbA1C, RBS, and BMI in both groups.

The frequency of AN (outcome variable) was compared between the two groups (cases and controls) using the Chi-square test. Stratification of data was done for gender, obesity, and age, and post-stratification Chi-square test was applied to assess effect modifiers. Comparisons were also made for baseline parameters (gender, obesity, age, HbA1C, RBS, and BMI) using the Student's t-test for continuous variables and the Chi-square test for categorical variables to assess comparability of results. A p-value ≤0.05 was considered statistically significant for all analyses. Bias and confounders were controlled by strictly adhering to inclusion and exclusion criteria and through stratification.

RESULTS

The study included 200 participants, comprising 100 diagnosed cases of Type 2 diabetes mellitus and 100 healthy controls. The mean age of participants was 46.0 ± 9.0 years, with a slightly higher mean among cases (47.2 ± 9.1) compared to controls (44.8 ± 8.7). Males represented 54% of the total sample, while females constituted 46%. The majority of participants resided in urban areas—60% among cases and 58% among controls (Table 1).

The frequency of Acanthosis Nigricans (AN) was significantly higher among diabetic participants (25%) than controls (4%) ($p < 0.001$, Chi-square test). The odds of having AN were 8.33 times higher in diabetics compared to non-diabetics (OR = 8.33, 95% CI = 2.70–25.65) (Table 2). Overall, AN was present in 14.5% of the total study population.

Comparison of anthropometric and biochemical parameters demonstrated that participants with AN had higher mean BMI (29.6 ± 3.4 kg/m²), waist circumference (102.5 ± 8.6 cm), random blood sugar (186.4 ± 45.8 mg/dl), and HbA1c (7.9 ± 1.1%) compared to those without AN ($p < 0.001$ for all, independent t-test) (Table 3). When stratified by obesity, 72.4% of individuals with AN were obese (BMI ≥ 28 kg/m²) compared to 29.2% without AN ($p < 0.001$, Chi-square test). The odds of AN among obese individuals were 6.47 times higher than among non-obese participants (OR = 6.47, 95% CI = 2.66–15.75) (Table 4). Stratification by age showed that AN was more prevalent in participants aged ≥ 40 years (69%) than those < 40 years (31%) ($p = 0.03$, Chi-square test), whereas gender did not show a significant association ($p = 0.91$) (Table 5)

Table 1: Demographic Characteristics of Study Participants (n = 200).

Variable	Cases (Diabetes) n=100	Controls (non-diabetes) n=100	Total n=200
Age (years), Mean ± SD	47.2 ± 9.1	44.8 ± 8.7	46.0 ± 9.0
Male (%)	56 (56%)	52 (52%)	108 (54%)
Female (%)	44 (44%)	48 (48%)	92 (46%)
Urban residence (%)	60 (60%)	58 (58%)	118 (59%)

Table 2: Frequency of Acanthosis Nigricans in Study Participants

Acanthosis Nigricans	Cases (n=100)	Controls (n=100)	Total (n=200)
Present (Yes)	25 (25%)	4 (4%)	29 (14.5%)
Absent (No)	75 (75%)	96 (96%)	171 (85.5%)

Table 3: Comparison of Anthropometric and Biochemical Parameters Between Groups.

Obesity (BMI ≥28 kg/m²)	AN Present (n=29)	AN Absent (n=171)	Total (n=200)	p-value
Yes	21 (72.4%)	50 (29.2%)	71 (35.5%)	<0.001
No	8 (27.6%)	121 (70.8%)	129 (64.5%)	

Table 4Association Between Acanthosis Nigricans and Obesity:

Parameter	Cases with AN (n=25)	Cases without AN (n=75)	Controls (n=100)	p-value
BMI (kg/m²), Mean ± SD	29.6 ± 3.4	26.2 ± 2.8	24.8 ± 3.1	<0.001
Waist Circumference (cm)	102.5 ± 8.6	95.4 ± 7.1	88.7 ± 6.8	<0.001
Random Blood Sugar (mg/dl)	186.4 ± 45.8	158.2 ± 39.3	92.4 ± 11.5	<0.001
HbA1c (%)	7.9 ± 1.1	6.8 ± 0.9	5.4 ± 0.5	<0.001

Table 5: Stratification of Acanthosis Nigricans by Age and Gender.

Variable	AN Present n=29	AN Absent n=171	Total n=200	p-value
Age <40	9 (31%)	89 (52%)	98	0.03
Age ≥40	20 (69%)	82 (48%)	102	
Male	16 (55%)	92 (54%)	108	0.91
Female	13 (45%)	79 (46%)	92	

DISCUSSION

This case–control study demonstrated a significant association between Acanthosis Nigricans (AN) and Type 2 Diabetes Mellitus (T2DM) in adults from District Shangla, Pakistan. The findings reaffirm that AN is more frequent among individuals with T2DM and is closely linked with adverse metabolic indicators such as higher BMI, waist circumference, HbA1c, and random blood sugar (RBS). These results support the concept that AN reflects underlying insulin resistance and metabolic dysregulation. Our findings are consistent with regional and international evidence linking AN with poor glycemic control and obesity.

A study conducted in Lahore (2025) reported a similar pattern—greater BMI and AN prevalence in diabetic individuals—and recognized AN as a visible marker of insulin resistance.[11] Wang et al. (2023) further emphasized the importance of central adiposity, showing that "waist-corrected BMI" predicts diabetes better than BMI alone.[12] Likewise, studies evaluating central obesity indices, such as those from Ethiopia, demonstrated that waist circumference and waist-to-height ratio outperform BMI in predicting poor glycemic control.[13]

The observed strong association between AN and waist circumference in our population supports these findings, indicating that central fat accumulation plays a pivotal role in AN pathogenesis. From a mechanistic perspective, AN arises in states of hyperinsulinemia, where excessive insulin or IGF-1 receptor activation stimulates epidermal proliferation.[15] The high proportion of obesity among AN-positive participants in our study (~72.4%) reinforces this biological link, suggesting that AN may act as a visible manifestation of systemic metabolic overload.

Older age also appeared to modify this association, likely reflecting cumulative metabolic burden and longer disease duration. This is in line with regional findings, such as the Lahore study, which reported higher age among AN-positive diabetics.[11] The lack of gender difference in our results indicates that metabolic factors (obesity, insulin resistance, glycemic control) may outweigh sex-related influences on AN

development. While some studies report subtle gender differences, others—especially in South Asian settings—similarly find no significant sex-based variation. The novelty of this study lies in its focus on a Pakistani subpopulation from a semi-rural district, where ethnic, dietary, and lifestyle factors differ from urban or Western populations.

To our knowledge, no previous research from Shangla or similar Khyber Pakhtunkhwa districts has explored AN–diabetes association. Given genetic predispositions, variable obesity thresholds, and differing environmental exposures, our findings contribute important local evidence that may improve early diabetes recognition in resource-limited clinical settings. Clinically, AN represents a low-cost, non-invasive indicator that can aid primary care physicians in identifying individuals at risk for metabolic abnormalities. This is particularly relevant in Pakistan, where limited access to laboratory investigations often delays diagnosis. Detecting AN during routine physical examinations can prompt timely metabolic screening, potentially improving early detection and prevention of diabetes-related complications.

However, causality cannot be inferred from this case–control design. The direction of association—whether AN precedes or follows insulin resistance—cannot be determined. Moreover, hospital-based sampling may have introduced selection bias, and the absence of direct insulin resistance measures (e.g., HOMA-IR, fasting insulin) limits mechanistic interpretation. The BMI ≥28 kg/m² criterion, although adapted from Asian cutoffs, may not fully capture ethnic differences in body composition. Future studies should employ longitudinal or cohort designs to evaluate temporal relationships between AN onset and glycemic deterioration. Incorporating insulin sensitivity indices and body fat distribution analyses (via imaging or biomarkers) could provide a more precise understanding of the AN–T2DM pathway. Additionally, interventional studies evaluating whether weight reduction or improved glycemic control leads to regression of AN could help establish its value as a clinical monitoring marker.

CONCLUSION

This study strengthens the evidence that AN is a clinically useful marker associated with obesity, large waist circumference, poorer glycemic control, and older age among persons with T2DM. While not universal, its presence should prompt clinicians to assess metabolic risk more closely, particularly in low-resource settings.

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