

Acanthosis Nigricans in Patients with Type II Diabetes Mellitus at a Tertiary Care Hospital of Lahore

Nauman Ismat Butt, Khalid Mahmood, Nimra Kanwal, Fahmina Ashfaq

ABSTRACT

Objective: Acanthosis Nigricans is characterized by skin thickening with hyperpigmentation dermatosis predominantly seen on flexural aspects & nape of neck. The objective of present study was to determine frequency of Acanthosis Nigricans among patients of type II diabetes mellitus.

Study Design and Setting: This observational cross-sectional study was undertaken at Department of Medicine Azra Naheed Medical College, Superior University Lahore from August 2021 to April 2022.

Methodology: Type II diabetes mellitus was defined as patients with HbA1c 7.0%, or two blood glucose random readings of ≥ 200 mg/dl, or previous history of diabetes diagnosis, or taking anti-hyperglycemic medicines. Acanthosis Nigricans was defined as >2 cm poorly defined hyperpigmented skin lesions of brownish black color and velvety appearance present over the nape of neck, axillae and/or groin. Patients with non-diabetic causes of Acanthosis Nigricans were excluded. After informed consent, 340 patients of type II diabetes mellitus aged 30-75 years of both gender were enrolled using non-probability consecutive sampling technique. Demographic information was noted and the patients were examined for Acanthosis Nigricans. Data was entered and analyzed by SPSS version 20.0.

Results: Mean age was 48.2 ± 13.8 years with 187 (55.0%) females. The mean height, weight and BMI were 1.5 ± 0.3 meters, 57.8 ± 11.6 kilograms and 28.8 ± 9.5 kg/m² respectively. The mean duration of disease was 44.2 ± 9.3 months and Acanthosis Nigricans was seen in 86 (25.2%). Acanthosis Nigricans was not significantly associated with age, gender, BMI or duration of disease.

Conclusion: Acanthosis Nigricans was present in almost a quarter of type II diabetes mellitus patients.

Key words: Acanthosis Nigricans, Insulin Resistance, Type II Diabetes Mellitus.

How to cite this Article:

Butt NI, Mahmood K, Kanwal N, Ashfaq F. Acanthosis Nigricans in Patients with Type II Diabetes Mellitus at a Tertiary Care Hospital of Lahore. J Bahria Uni Med Dental Coll. 2023;13(1):13-17 DOI: <https://doi.org/10.51985/JBUMDC202266>

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INTRODUCTION:

Type II Diabetes Mellitus is characterized by hyperglycemia due to pathological processes such as increased insulin resistance and/or reduced insulin secretion.¹ Rising worldwide and International Diabetes Federation estimates that up to 552 million people will be affected by diabetes by 2030.² Pakistan is one of the top 10 countries according to diabetes prevalence. Symptoms of marked hyperglycemia include

polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acanthosis Nigricans is characterized by skin thickening with hyperpigmentation dermatosis predominantly seen on flexural aspects and nape of neck.³ High insulin levels are thought to play a role in pathogenesis of Acanthosis Nigricans.⁴ By virtue of this association, it may be linked to increased risk for type II Diabetes Mellitus.⁵

The complications of diabetes affect nearly every tissue of the body and diabetes is a leading cause of cardiovascular morbidity and mortality, blindness, renal failure and amputations. Further, the early diagnosis of type 2 diabetes in adolescents and young adults (up to age 40 years) has been linked to a more aggressive form of the disease, with premature development of serious complications. Together, these sobering statistics underscore the vital importance of uncovering the root causes of diabetes and its complications in order to best design strategies for therapeutic intervention in this disorder. Patients with Acanthosis Nigricans due to diabetes generally suffer few or no skin complications and have a good prognosis with potentially complete resolution with adequate treatment and glycemic control. High-risk populations for development of Acanthosis

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Received: 30-Apr-2022
Accepted: 19-Dec-2022

Nigricans are African-Americans, Hispanics, and Native Americans, although this condition presents in all races. There are various studies that indicate different frequencies of several skin manifestations including Acanthosis Nigricans in type II diabetes mellitus and this variability maybe related to ethnicity.³ Litonjua et al. reported Acanthosis Nigricans in 52.6% African-Americans as compared to 35.9% in Latin-American⁶. Burke et al. demonstrated It to be in 41.1% in diabetics opposed to 31.6% in non-diabetics⁷. Grandhe et al. reported its frequency to be 62.6% in diabetes mellitus compared to 40% in controls⁸. One study from India demonstrated Acanthosis Nigricans in 5.9% of diabetes mellitus patients.⁹ Another study showed 11.6% prevalence in diabetics.¹⁰ Although studies have been unable to establish a distinct link of Acanthosis Nigricans with type II diabetes mellitus, its association with raised insulin levels is well studied in literature and this suggests the possibility of an association of these conditions indicating that patients with Acanthosis Nigricans may be at elevated risk to develop type II diabetes. Furthermore it may be recognized as a cutaneous marker in type II diabetes.

Given the variable but markedly high presence of Acanthosis Nigricans in diabetes mellitus, it may be used as a cutaneous marker for patients with type II diabetes mellitus. Whether ethnic differences play a role in pathophysiology of Acanthosis Nigricans in diabetes is not known. The association of acanthosis nigricans, diabetes mellitus, hyperinsulinemia and insulin resistance highlight importance of incorporating it as a clearly visible cutaneous marker of diabetes, identifying patients who are at risk to develop diabetes, and thereby helping patients to institute lifestyle modifications to avert this potentially life-altering disorder to reduce disease morbidity and disability. Furthermore, Acanthosis Nigricans may aid in identification of patients that already have developed diabetes but are undiagnosed as diabetes may remain asymptomatic initially. Diagnosing diabetes in the initial stages leads to early treatment and glycemic control thus reducing long-term diabetes complications. The rationale of our study was to document presence of Acanthosis Nigricans among type II diabetes mellitus patients presenting to Department of Medicine, Allama Iqbal Medical College, Jinnah Hospital Lahore Pakistan so as to provide evidence for Pakistani population and to reduce scarcity of local data.

METHODOLOGY:

Data collection was done after taking approval from Institutional Review Board of Azra Naheed Medical College, Superior University Lahore Pakistan. The present observational cross-sectional study was conducted to find out prevalence of Acanthosis Nigricans among patients of type II diabetes mellitus at Department of Medicine Jinnah Hospital, Allama Iqbal Medical College Lahore Pakistan from August 2021 to April 2022. Type II diabetes mellitus was defined as patients with HbA1c of greater than 7.0%,

or two blood glucose random readings of ≥ 200 mg/dl, or previous history of diabetes diagnosis, or taking anti-hyperglycemic medicines. Acanthosis Nigricans was defined as >2 cm poorly defined hyperpigmented skin lesions of brownish black color and velvety appearance present over the nape of neck, axillae and/or groin. A sample size of 340 was calculated with confidence level 95% and margin of error 5% taking expected frequency as 5.8% as reported by Khokharo et al.¹¹ Patients with non-diabetic causes of Acanthosis Nigricans (endocrine disorders such as acromegaly, hypothyroidism, polycystic ovarian syndrome, Cushing's disease; malignancies of liver, lung, gastrointestinal tract, uterus; and drugs such as corticosteroids, nicotinic acid, oral contraceptives), pregnant females and patients already on treatment for Acanthosis Nigricans as assessed by detailed history and examination were excluded from the study.

After obtaining written informed consent, 340 patients of type II diabetes mellitus (both new cases and previously diagnosed as per operational definition) aged 30-75 years of both genders were included in the study using non-probability consecutive sampling technique. Demographic information including age, gender, weight, height, BMI and duration of disease were noted and the patients were examined for Acanthosis Nigricans. Data was entered and analyzed by SPSS version 20.0. Mean and standard deviation were calculated for quantitative variables like age, BMI (the WHO and NIH guidelines for Asian individuals define overweight as a BMI between 23 and 24.9 kg/m² and obesity as a BMI >25 kg/m²) and duration of disease¹². Frequency and percentage were calculated for qualitative variables like gender. Data was stratified to address effect modifiers by using Chi-square test with p-value <0.05 as significant.

RESULTS:

A total of 340 patients were enrolled in this study having mean age of 48.2 \pm 13.8 years with 153 (45.0%) males and 187 (55.0%) females as shown in Table 1. Ninety-two (27.1%) patients were <52 years of age while 248 (72.9%) patients were aged >53 years. The mean height, weight and BMI of the patients were 1.5 \pm 0.3 meters, 57.8 \pm 11.6 kilograms and 28.8 \pm 9.5 kg/m² respectively. Normal BMI was seen in 132 (38.8%) patients while 208 (61.2%) patients were overweight and obese. The mean duration of disease was 44.2 \pm 9.3 months with 213 (62.6%) patients having >24 months disease duration. In our study, Acanthosis Nigricans was seen in 86 (25.2%) patients as shown in Table 1. Stratification of data according to Acanthosis Nigricans is shown in Table 2.

In our study, Acanthosis Nigricans did not have a statistically significant association with age (p-value: 0.091), gender (p-value: 0.753), BMI (p-value: 0.833) or duration of disease (p-value: 0.360) as shown in Table 2.

Table 1: Demographic and Clinical Variables of the Patients

| | |
|------------------------------|----------------------------|
| Mean Age | 48.2+13.8 years |
| Mean Height | 1.5+0.3 meters |
| Mean Weight | 57.8+11.6 kilograms |
| Mean BMI | 28.8+9.5 kg/m ² |
| Mean Duration of Disease | 44.2+9.3 months |
| Age Groups: | |
| 30-52 years | 92 (27.1%) |
| 53-75 years | 248 (72.9%) |
| Gender: | |
| Male | 153 (45.0%) |
| Female | 187 (55.0%) |
| BMI: | |
| 17-24 kg/m ² | 132 (38.8%) |
| >25 kg/m ² | 208 (61.2%) |
| Duration of disease: | |
| <24 months | 127 (37.4%) |
| >24 months | 213 (62.6%) |
| Acanthosis Nigricans: | |
| Present | 86 (25.2%) |
| Absent | 254 (74.8%) |

Table 2: Stratification of Demographic and Clinical Variables with regards to Acanthosis Nigricans

| Demographic and Clinical Variables | Acanthosis Nigricans | | p-value |
|--------------------------------------|----------------------|-------------|---------|
| | Present | Absent | |
| Age (years): | | | |
| 30-52 | 37 (24.1%) | 116 (75.9%) | 0.091 |
| 53-75 | 49 (26.3%) | 138 (73.7%) | |
| Gender: | | | |
| Male | 16 (17.3%) | 76 (82.7%) | 0.753 |
| Female | 70 (28.2%) | 178 (71.8%) | |
| BMI (kg/m²): | | | |
| 17-24 | 34 (25.7%) | 98 (74.3%) | 0.833 |
| >25 | 52 (25.0%) | 156 (75.0%) | |
| Duration of disease (months): | | | |
| <24 | 37 (29.2%) | 90 (70.8%) | 0.360 |
| >24 | 49 (23.0%) | 164 (77.0%) | |

DISCUSSION:

In our study with 340 patients of type II diabetes mellitus, Acanthosis Nigricans was seen in 86 (25.2%). Khokharo et al. showed Acanthosis Nigricans in 5.8% diabetes patients from Sindh¹¹. In Karachi, Niaz et al. found Acanthosis Nigricans in 20% patients of diabetes with higher incidence in females and patients with poor diabetes control¹². In Battagram Khyber Pakhtunkhwa, Ahmed et al. reported Acanthosis Nigricans in 2.9% of diabetes patients¹⁴. In Ludhiana India, Deepika et al. reported prevalence of Acanthosis Nigricans as 10.9% in diabetics¹⁵. There is a

great variability in its prevalence in type II diabetes mellitus and these differences may be related to ethnicity even in the residents of a same geographical area which was also the case with results of our study.

Although studies have been unable to establish a distinct link of Acanthosis Nigricans with type II diabetes mellitus, its association with raised insulin levels is well studied literature and this suggests the possibility of an association of these conditions indicating that patients with Acanthosis Nigricans may be at elevated risk to develop type II diabetes. Furthermore, it may be recognized as a cutaneous marker in type II diabetes. It has been found in many studies that Acanthosis Nigricans is associated with insulin resistance or hyperinsulinemia, which are considered to be the major factors in the pathophysiology of type 2 diabetes, in a large number of patients.^{5,16} Kobaissi et al. studied a population of overweight Hispanic children to determine if there was a relationship between Acanthosis Nigricans and insulin sensitivity, independent of the fat content of the body, and found that it was indeed an independent risk factor for the development of insulin resistance¹⁶. Kong et al. found that patients with this skin condition were almost twice as likely to have type 2 diabetes compared with patients without it, after controlling for age, BMI, and several other risk factors for type 2 diabetes including race, hypertension and family history of type 2 diabetes⁵. A high prevalence of this skin condition was also found in a population of the native Americans of Texas and Nebraska by Stuart et al. who concluded that presence of Acanthosis Nigricans in this population suggested the presence of insulin resistance and therefore its clinical detection may help to identify individuals who are at a high risk for developing the disease¹⁷. In our study, Acanthosis Nigricans was seen in 52 (25.0%) of overweight and obese patients as compared to 34 (25.7%) patients with normal BMI. Furthermore Acanthosis Nigricans was not significantly associated with age (p-value: 0.091), gender (p-value: 0.753), BMI (p-value: 0.833) or duration of disease (p-value: 0.360).

While the goal of therapy is to treat the primary cause, cosmetic resolution of Acanthosis Nigricans lesions can be important for patients and their quality of life. Treatment options for Acanthosis Nigricans have not been extensively studied; however, smaller powered clinical trials and case reports exist in the literature.¹⁸ Patients with Acanthosis Nigricans due to diabetes generally suffer few or no skin complications and have a good prognosis with potentially complete resolution with adequate treatment and glycemic control.¹⁹ It can fade over time with treatment of insulin resistance and controlling blood glucose by diet and exercise as weight loss and correction of insulin resistance reduces the hyperkeratotic lesions.²⁰ Topical ointments using keratolytics like topical retinoids and podophyllin may aid in lightening skin in selected patients mainly for cosmetic reasons.²¹ Topical vitamin D analogs reduce keratinocyte

proliferation and may improve lesions of Acanthosis Nigricans.²² However success rates of topical treatments is variable. Other agents that have been tried include metformin, rosiglitazone, melatonin and etretinate.²³ Octreotide also has been shown to improve Acanthosis Nigricans in insulin resistance. While these studies have the potential to shed light on its therapy, clinical trials are needed to examine topical and oral treatment options specifically for the improvement of skin lesions. The current literature that exists is limited, and higher powered studies with larger patient populations are needed to further elucidate the Acanthosis Nigricans treatment paradigm.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β -cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action.² The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues.¹ Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.³ The complications of diabetes affect nearly every tissue of the body and diabetes is a leading cause of cardiovascular morbidity and mortality, blindness, renal failure and amputations. Further, the early diagnosis of type 2 diabetes in adolescents and young adults (up to age 40 years) has been linked to a more aggressive form of the disease, with premature development of serious complications. Together, these sobering statistics underscore the vital importance of uncovering the root causes of diabetes and its complications in order to best design strategies for therapeutic intervention in this disorder. Type II Diabetes Mellitus, characterized by hyperglycemia due to pathological processes such as increased insulin resistance and/or reduced insulin secretion,¹ rising worldwide and International Diabetes Federation estimates that up to 552 million people will be affected by diabetes by 2030.² Pakistan is one of the top 10 countries according to diabetes prevalence.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision.¹ Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.² Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual

dysfunction.²⁴

There are a few limitations of our study as well. Our study is a descriptive non-randomized cross-sectional study and therefore limited due to patient selection bias. A single center-based study having a relatively small sample size, our results may not be generalized to general population. Our study should be used as a stepping stone based on which further studies should be conducted to collect further evidence. The association of Acanthosis Nigricans, diabetes mellitus, hyperinsulinemia and insulin resistance highlight importance of incorporating it as a clearly visible cutaneous marker of diabetes, identifying patients who are at risk to develop diabetes, and thereby helping patients to institute lifestyle modifications to avert this potentially life-altering disorder to reduce disease morbidity and disability. Furthermore Acanthosis Nigricans may aid in identification of patients that already have developed diabetes but are undiagnosed as diabetes may remain asymptomatic initially. Diagnosing diabetes in the initial stages leads to early treatment and glycemic control thus reducing long-term diabetes complications. With more information on therapies that treat the underlying causes of Acanthosis Nigricans, as well as treatment options for the cosmetic appearance of lesions, providers will have the opportunity to treat patients underlying diseases and the psychological consequences of the Acanthosis Nigricans to improve patient quality of life.

CONCLUSION:

We found Acanthosis Nigricans to be present in a quarter of patients with type II diabetes mellitus amongst our sample population. Acanthosis Nigricans was not significantly associated with age, gender, BMI or duration of disease in the present study. However still the its presence in some patients with diabetes mellitus highlight importance of incorporating it as a clearly visible cutaneous marker of diabetes, identifying patients who are at risk to develop diabetes, and thereby helping patients to institute lifestyle modifications to avert this potentially life-altering disorder to reduce disease morbidity and disability.

Authors Contribution:

Nauman Ismat Butt: Conception and design, Analysis and interpretation of the data, Literature review and drafting of the article

Khalid Mahmood: Collection and assembly of data, Critical review and revision of the article

Nimra Kanwal: Conception and design, Literature review and drafting of the article

Fahmina Ashfaq: Collection and assembly of data, Critical review and revision of the article

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