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Original Article

Screening for Acanthosis Nigricans in Type 2 Diabetes Mellitus - It's Time for Reinforcement

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Abstract

Background: Acanthosis nigricans is a well-known external marker for insulin resistance, obesity and type 2 diabetes mellitus (T2DM). The prevalence of acanthosis varies among different ethnic groups.

Aim: The aim of the study was to study the prevalence and relationship of acanthosis nigricans with age, body mass index (BMI), and other risk factors in T2DM.

Methods: A total of 300 patients with T2DM attending the medical outpatient department in a tertiary care teaching hospital were included in the study. Their demographic and clinical parameters were recorded. The presence of acanthosis nigricans, its severity and relationship with other diabetic risk factors were assessed.

Results: Among the 300 patients enrolled in study 187 patients had evidence of acanthosis of varied severity. 172 were female patients. The mean BMI was 28.8 kg/sq m and mean waist circumference was 97.5 cm. Significant association ($P < 0.005$) of acanthosis nigricans was noted with younger age, female sex, overweight, and obesity. Similar significance was also noted with hypertension and dyslipidemia. However, the duration of T2DM, previous history of CVA or coronary artery disease, family history of T2DM did not bear a significant association with the presence of acanthosis.

Conclusion: The high prevalence of acanthosis nigricans in T2DM patients favors it as a potential screening tool in the T2DM risk assessment.

Key words: Acanthosis nigricans, Insulin resistance, Obesity, Type 2 diabetes mellitus

INTRODUCTION

India is turning a diabetic capital in incidence and prevalence of diabetes and its related adverse health issues are causing resource wastage.[1,2] Having such a huge burden of the disease, the availability of screening tests that are affordable, safe and sensitive are the need of the hour. Acanthosis nigricans (AN) is one such recommended screening tool.[3] Its association with hyperinsulinemia, insulin resistance, Type 2 diabetes mellitus (T2DM), and obesity is well established.[4-6] Various studies have shown varying prevalence of AN among different ethnic groups, darker races have higher incidences than the whites.[7] In a study by Grandhe *et al.*, AN was seen in up to two-thirds of T2DM patients in North India.[8]

This study aims to know the prevalence of AN among T2DM patients and its relationship with anthropometric measurements and other risk factors for T2DM.

METHODS

A total of 300 T2DM as per the WHO criteria[9] attending the medical outpatient department were enrolled in the study. People with other known conditions associated with AN such as internal malignancies and autoimmune diseases such as systemic lupus erythematosus, scleroderma, Sjogren's syndrome, Hashimoto's thyroiditis, history of intake of oral contraceptive pills, and usage of topical Fusidic acid[5,7] were excluded from the study.

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Demographic and clinical parameters including anthropometric measurements were recorded in a pre-structured pro forma. Apart from demographic data, history of dyslipidemia, systemic hypertension, coronary artery disease and/or cerebrovascular accident, duration and treatment of T2DM, and family history of T2DM were recorded. Anthropometric measurements such as weight, height, body mass index (BMI), waist and hip circumference, and waist-hip ratio were measured. Waist circumference was recorded midway between iliac crest and lower margins of ribs. Hip circumference was measured at the maximum circumference of the buttocks. Body mass index was measured by Quetelet's index (weight in kilograms divided by height in meters squared). BMI of ≥23 kg/m^2 was considered overweight for both men and women in the study population.[6] All the study group subjects were examined for the presence of AN at the neck and other sites. Its severity and texture were graded as described by Burke *et al.*[10] According to this scale, Grade 0 - not visible on close inspection, Grade 1 - clearly present on close visual inspection, Grade 2 - limited to base of skull but does not extend to the lateral margins of the neck, Grade 3 - extending to the lateral margins of the neck but not visible from the front, and Grade 4 - extending to the anterior aspect of the neck. The texture of AN is graded from 0 to 3 as Grade 0 - smooth to touch with no differentiation from normal skin on palpation, Grade 1 - rough to touch, clearly differentiated from normal skin, Grade 2 - coarseness can be observed visually with portions of skin clearly raised above other areas, and Grade 3 - extremely coarse, hills and valleys appearance on examination. Other sites where AN can appear such as the knuckles, elbows, axillae, and knees were also examined and documented. The presence and severity of AN were assessed by a single trained observer.

The recent HbA1c was taken as a surrogate marker for glycemic control.

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. The proportion is computed for categorical data. Chi-square test has been used to find the statistical significance between two groups of proportions. The mean and standard deviation is computed for continuous data. The independent *t*-test was used to find statistical significance between the groups of mean. Correlation coefficient was computed to assess the linear relationship between continuous variables. All analyses were two-tailed, and $P \leq 0.05$ was considered significant. SPSS version 16.0 was used for data analysis.

RESULTS

Acanthosis nigricans was observed among 62.33% of the study patients. Table 1 shows the demographic characteristics of the study group. 33.67% of female patients had AN as compared to 28.67% of male patients. The prevalence of AN was inversely proportional to the age group. AN was seen in 96.15% (25 out of 26) in the age group 25–30 years while 31.48% (17 out of 54) of patients in the age group of >70 years had AN. The prevalence of AN was directly proportional to the BMI of the patients. It was seen in 56.56%, 61.85%, and 68.26% among the normal BMI, overweight, and obese patients, respectively. 69.56% of patients with central obesity had evidence of AN as compared to 50.86% of patients without central obesity. Similarity higher prevalence of AN was seen in patients with a history of systemic hypertension and dyslipidemia as compared to their absence (64.95% and 65.48% vs. 55.81% and 56.31%). The incidence of acanthosis nigricans was higher among uncontrolled diabetic patients than those with well-controlled diabetic patients (78.87% vs. 21.83%).

Table 2 shows the severity of acanthosis at the nape of the neck and other sites.

The nape of the neck was involved among all the patients with evidence of acantosis nigricans (100%) followed by axilla (71.65%), cubital fossa (32.62%), popliteal fossa (24.06%), knuckles (18.18%), and other areas (6.95%) being groin, and dorsum of toes and flanks. Table 3 shows the comparison of anthropometric parameters and comorbid conditions in subjects with or without AN. Although females seemed to have a higher incidence of AN, the values were not statistically significant. Higher levels of BMI, waist circumference, hip circumference, and waist-to-hip ratio were noticed among the AN group. The incidence of AN was significantly higher among uncontrolled diabetic patients with long-standing history of diabetes mellitus. The presence of comorbidities such as dyslipidemia and systemic hypertension was also higher among the patients with AN. Table 4 shows the comparison of the anthropometric variables with varying severity of acanthosis nigricans. There is a steady increase in the severity of acanthosis as the anthropometric variables increased, which was statistically significant.

DISCUSSION

The burden of diabetes is increasing exponentially, so is obesity. Hence, adjuvant sensitive screening tools for patients with T2DM for early identification are essential. As most of the T2DM patients are obese, BMI forms a major confounder in the association of AN with T2DM. This study highlights the presence of AN as a sensitive screening tool for T2DM.

AN is "a symmetric eruption characterized by hyperpigmented, velvety cutaneous thickening that can

Table 1: Demographic and clinical characteristics

Characteristics	Subgroup	Frequency of characteristics *n*=300 (%)	Prevalence in AN group *n*=187 (%)
Age in years	25–39	26 (8.67)	25 (13.37)
	40–49	41 (13.67)	41 (21.93)
	50–59	91 (30.33)	62 (33.15)
	60–69	88 (29.33)	42 (22.46)
	≥70	54 (18)	17 (9.09)
Sex	Males	128 (42.67)	76 (40.64)
	Females	172 (57.33)	111 (59.35)
Body mass index (kg/sq.m)	Normal	99 (33)	56 (29.95)
	Overweight	97 (32.33)	60 (32.09)
	Obese	104 (34.67)	71 (37.97)
Waist circumference (cm)	Normal	116 (38.67)	59 (31.55)
	Central obesity	184 (61.33)	128 (68.45)
Waist-hip ratio	Normal	122 (40.67)	64 (34.22)
	Increased	178 (59.33)	123 (65.77)
Duration of T2DM	<5 years	57 (19)	24 (12.83)
	5–10 years	138 (46)	95 (50.80)
	>10 years	105 (35)	68 (36.36)
Family history of T2DM	Yes	248 (82.67)	149 (79.68)
	No	52 (17.33)	38 (20.32)
Systemic hypertension	Yes	214 (71.33)	139 (74.33)
	No	86 (28.67)	48 (25.67)
Dyslipidemia	Yes	197 (65.67)	129 (68.98)
	No	103 (34.33)	58 (31.01)
CAD/CVA	Yes	188 (62.67)	92 (49.19)
	No	112 (37.33)	95 (50.80)
Treatment modality	OHAS	174 (58)	92 (49.19)
	Insulin	36 (12)	31 (16.57)
	OHAS and insulin	90 (30)	64 (34.22)
Glycemic control	Uncontrolled	213 (71)	168 (89.83)
	Good control	87 (29)	19 (10.16)

T2DM: Type 2 diabetes mellitus, CAD: Coronary artery disease

Table 2: Acanthosis nigricans severity at the nape of neck and other sites

Severity of AN	No. at nape of neck *n*=187 (%)	No. of AN at other sites (%)
Grade 1	71 (37.96)	31 (16.57)
Grade 2	56 (29.94)	29 (11.76)
Grade 3	52 (27.80)	25 (13.36)
Grade 4	8 (4.27)	3 (1.60)

Table 3: Comparison of anthropometric and comorbid characteristics among diabetic patients with or without acanthosis nigricans

Parameter	AN no. *n*=187 (%)	No AN no. *n*=113 (%)	*P* value
Sex			
Male	76 (40.64)	52 (46.01)	0.068
Female	111 (59.36)	61 (53.98)	
Duration of T2DM	9.2±3.18	5.6±2.42	0.04
BMI	28.3±2.04	23.4±1.74	0.000
Waist circumference	96.4±5.6	86.6±5.3	0.000
Waist-hip ratio	0.99±0.074	0.92±0.052	0.002
Glycemic control			
Uncontrolled	168 (89.83)	77 (68.14)	<0.000
Good	19 (10.16)	68 (60.17)	
Dyslipidemia			
Present	129 (68.98)	68 (60.17)	0.063
Absent	58 (31.01)	46 (40.707)	
SHT			
Present	139 (74.33)	75 (66.37)	0.004
Absent	48 (25.67)	38 (33.62)	

occur on any part of the body."[5] It can develop anywhere on the skin most frequently involving the neck, axilla, cubital and popliteal fossae, knuckles, and inner aspects of thighs. Traditionally, AN can be sub-grouped as three forms. They are:

i. Idiopathic form - in healthy children
ii. Paraneoplastic form - in patients with internal malignancy
iii. In obese patients with or without endocrine disorders - this was previously known as pseudoacanthosis nigricans.

It is considered a marker of insulin resistance and hyperinsulinemia and a risk factor for T2DM.[3,4,11] The pathogenesis could be explained by high levels of insulin activating the dermal and epidermal cells - the fibroblasts and keratinocytes, respectively, through the insulin-like growth factor receptors present on these cells. This, in turn, results in increased glycosaminoglycan deposition in the

Table 4: Comparison of anthropometric variables with the severity of AN

Variable	Grade 1 AN no.	Grade 2 AN no.	Grade 3 AN no.	*P* value
BMI	27.4±2.58	28.5±2.14	32.7±1.687	0.000
Waist circumference	93.5±5.6	98.2±4.82	102.8±3.78	0.001
Waist-hip ratio	0.98±0.032	0.99±0.027	1.01±0.0198	0.002

BMI: Body mass index

dermis leading to papillomatosis mediated by fibroblasts and keratinocyte proliferation causing hyperkeratosis and acanthosis.[8]

ADA recommends AN as part of T2DM risk assessment criteria for children and adolescents.[12] Our study throws light on AN as a good marker of T2DM even for the adult population. However, despite decreasing prevalence with age, AN was still prevalent in older groups. The higher prevalence of AN in younger diabetic patients could be explained by the fact that obesity was more prevalent among the younger patients. Previous studies showed BMI and fasting insulin levels correlated with AN severity at the nape of the neck.

The AN prevalence was higher among both males and females with 59.37% and 64.53%, respectively. The slight female predominance could be explained by the fact that polycystic ovarian syndrome (PCOS), an established insulin resistant state could have accounted for some of the higher prevalence of AN among diabetic women.[13]

In the present study, 34.67% and 32.33% of the diabetic population were obese and overweight, respectively. Among them, 68.26% and 61.85% demonstrated the presence of AN. Normal weight patients were 33%, and AN was noticed in 56.56% of these patients. These percentages show greater insulin resistance with patients having AN and obesity in combination than with obesity alone,[14] so the presence of AN in an obese patient should prompt the suspicion of T2DM. The mere fact that 56.56% of normal weight patients had evidence of AN tells that AN could be a valuable marker of T2DM even in the low-risk groups.

Among the study population 62.33% had evidence of AN at the neck with or without AN at other sites, which were similar to the observations made in the previous studies.[10,15] In addition to a significant association between AN and BMI, other anthropometric measurements such as waist circumference and waist-hip ratio also showed significant association with AN prevalence. This was also observed with progressing severity of AN. Higher prevalence of AN was also found among patients with hypertension and dyslipidemia.

Thus, AN can serve as a valuable tool for improved detection of not just undiagnosed T2DM but also a significant predictor of future T2DM. This was also described by Stuart *et al*.[16] Therefore presence of AN, mandates early lifestyle modifications to prevent T2DM and its complications.

Limitations

The specificity of AN as a valuable tool to predict T2DM could not be ascertained in the present study as it was conducted among diabetic patients. We did not include a screening of acanthosis among prediabetic patients which could have answered this question. The study population was sampled from tertiary care teaching hospital which could be representing more severe forms of T2DM.

CONCLUSION

Acanthosis nigricans is highly prevalent across age groups and both sexes among the diabetic patients. The simplicity and convenience in assessing acanthosis nigricans favors its implementation as a valuable screening and risk assessment tool for T2DM. Therefore, proactive screening for AN in clinical practice should be strongly recommended, and the presence of AN should prompt a clinical suspicion of T2DM.

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