Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2022;31:101-104
doi: 10.15570/actaapa.2022.15

Insulin resistance in various grades of acanthosis nigricans

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Abstract

Introduction: Insulin resistance (IR) is a metabolism disorder that contributes to the pathophysiology of acanthosis nigricans (AN). In turn, AN is a self-determining risk factor and cutaneous marker of IR. However, conflicting evidence makes the AN–IR relationship debatable and open to exploration. If established, it could provide opportunities for early diagnosis and management of IR before the onset of diabetes mellitus and its complications by screening AN patients. This study investigates the prevalence of IR among AN patients and evaluates the association between IR and AN severity.
Methods: Eighty-seven patients, 18 to 60 years old, with untreated AN and absence of diabetes mellitus, underwent detailed history, systemic, and cutaneous examinations, as well as measurement of their body mass index (BMI), waist and hip circumference and their ratio (WHR), fasting blood glucose (FBG) and lipid profile, fasting serum insulin levels, and quantitative insulin-sensitivity check index (QUICKI). Severity of the neck lesions was graded according to Burke et al.'s grading system.
Results: AN was noted most commonly in younger age groups with 93.1% of the cases younger than 45. All patients had lesions on the neck, and 63.3% of the cases had multiple site involvement. Nearly 84% of the cases were overweight or obese. AN grades exhibited a significant positive association with BMI ($p = 0.002$) and WHR ($p = 0.016$). High IR (< 0.35 QUICKI) was seen in 55 (63.2%) AN patients. IR, QUICKI, and triglyceride levels showed no significant association with AN severity and the number of AN lesion sites ($p > 0.05$). LDL levels ($p = 0.02$) and WHR ($p = 0.049$) showed a significant positive association with the number of AN lesion sites, but not with AN severity grading ($p > 0.05$).
Conclusions: IR is present in AN patients, but the association between IR and AN severity is not significant enough to qualify AN as a screening tool for IR.

Keywords: acanthosis nigricans, insulin resistance, skin disease, obesity, diabetes mellitus

Received: 8 July 2022 | **Returned for modification:** 6 September 2022 | **Accepted:** 12 September 2022

Introduction

Acanthosis nigricans (AN) is a papillomatous dermatosis characterized by hyperpigmented, hyperkeratotic, velvety plaques, predominantly seen on the intertriginous surfaces of the neck, axilla, groin, and other sites (1, 2). The prevalence ranges from 7 to 74%, depending on age and race, as well as coexistent obesity and endocrinopathy (3, 4). Among the numerous factors that have been proposed as involved in the etiology and pathogenesis of AN are insulin-like growth factors (IGF), raised serum insulin levels, fibroblast growth factor (FGF) defects, transforming growth factor-α (TGF-α), perspiration and friction, drugs such as systemic corticosteroids, testosterone and exogenous estrogens including oral contraceptives, nicotinic acid, and fibroblast growth factor receptor ligands such as palifermin (3, 5).

AN lesions histopathologically show epidermal and/or dermal hyperplasia, orthokeratosis, and papillomatosis of the stratum spinosum with the basal layer showing hyperpigmentation without melanocytosis (5). AN is a reactive cutaneous response that is associated with obesity, insulin resistance (IR), endocrinopathy, and malignancies, especially gastrointestinal adenocarcinomas (5, 6).

IR, described as the inability of the body to respond appropriately to insulin, has now become a global epidemic (7). It leads to compensatory hyperinsulinemia (8). This excess insulin activates specific cell receptors such as insulin-like growth factor 1 receptors (IGF-1) in keratinocytes and fibroblasts leading to their proliferation, thus inducing the formation of AN plaques (9, 10).

Although IR is noted in AN patients, it is an independent risk factor (11). Cellular studies have revealed low numbers of insulin receptors on target cell surfaces and impaired receptor response to insulin in individuals with AN (8, 12). Moreover, AN has been known as a cutaneous marker of IR (10). In this prospective cohort study, sensitivity of 73.5%, specificity of 50%, a positive predictive value of 54.3%, a negative predictive value of 70%, and an accuracy level of 49% for AN to identify IR were observed (13). However, conflicting studies exist, providing evidence against this AN–IR relationship (14, 15).

This justifies exploring the relationship between AN and IR, which, if established conclusively, could provide opportunities to identify and manage IR early in its onset, before the development of outright diabetes mellitus and its associated complications by screening patients diagnosed with AN (6, 10).

Therefore, this study investigates the prevalence of IR among AN patients and evaluates the association between IR and AN severity.

Methods

This was a descriptive hospital-based clinical study conducted in the dermatology department at a tertiary care hospital in Bangalore, Karnataka, India, after receiving ethical approval from the institutional ethics committee. The sample size was calculated based on a study by Burke et al. (16), who observed that the average fasting insulin level was 12.6 µU/ml in the absence of AN (control group), 18.2 µU/ml in mild AN, and 26.0 µU/ml in severe AN.

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Accordingly, expecting a variation of 20%, in order to achieve 80% power and a 95% confidence interval with a 3.5 µU/ml difference between any groups considered clinically significant, the study required a minimum of 29 participants in each group. The study enrolled 87 patients, 18 to 60 years old, irrespective of their sex, with untreated AN and absence of diabetes mellitus. Patients with diabetes mellitus (type 1 and 2), polycystic ovary syndrome, and pregnant or lactating women were excluded from the study.

The patients' history was taken in detail regarding the onset, duration, extent, and sites of the lesions, family history of similar complaints, history of associated illnesses (diabetes mellitus, hypothyroidism, polycystic ovary syndrome, and hyperlipidemia), and amount of physical activity per week (physical activity for ≥ 5 days/week was considered high activity and < 5 days per week low activity) (17). Systemic examination was performed in all cases. Anthropometric parameters such as height and weight were measured by a single observer. Body mass index (BMI) was estimated as weight in kg / height in m², and patients were categorized based on the international classification with WHO cutoff (South Asian–specific cutoffs were not taken) as normal (18.5–24.9 kg/m²), overweight (25.0- 29.9 kg/m²), class 1 obesity (30.0–34.9 kg/m²), class 2 obesity (35.0–39.9 kg/ m²), or class 3 obesity (> 40 kg/m²) (18). Waist circumference (WC), hip circumference (HC), and waist/hip ratio (WHR) were calculated in a standard manner using flexible nonelastic tape, with an accuracy of 0.1 cm placed directly on the skin. The waist circumference was estimated at the midpoint between the edge of the iliac crest to the lateral costal margin with patients' arms alongside the body in a standing position (19). Cutoff values for WC were 85 cm and 80 cm in men and women, respectively, and those for WHR were 0.89 and 0.81 in men and women, respectively, among the Asian population (19).

All the cases underwent detailed cutaneous examination for the presence of skin tags and the site of the lesion (neck, axilla, knuckles, antecubital fossa, groin, popliteal fossa and mucosa, generalized, or any other site). Neck severity was graded according to the scale by Burke et al. as Grade 0 (absent), Grade 1 (present = present on close visual inspection, not visible to the casual observer, extent cannot be measured), Grade 2 (mild = restricted to the base of the skull, does not extend to the lateral margin of the neck, usually < 3 inches in breadth), Grade 3 (moderate = spreading to the lateral margins of the neck / posterior border of the sternocleidomastoid muscle, usually 3 to 6 inches wide, not visible from the front), and Grade 4 (severe = extending anteriorly, usually > 6 inches wide, visible on the front of the neck) (16).

Fasting blood glucose (FBG) was recorded for all patients with the hexokinase method, and values > 140 mg/dl implied elevated blood glucose levels whereas those > 126 mg/dl implied impaired blood glucose levels. Lipid profiling including measurement of serum triglyceride and low-density lipoprotein (LDL) levels was also performed. For measurement of fasting serum insulin levels, patients' whole blood samples were collected in a vacutainer using the standard venipuncture technique. The vacutainer was allowed to settle for 20 to 30 minutes, following which the tubes were centrifuged for 10 to 15 minutes at about 1,300 to 1,800 rpm, and then the serum was separated and transferred into test tubes and stored at –20 °C. Fasting serum insulin levels were measured with the Insulin (Serum) ELISA kit (Calbiotech, El Cajon, CA, USA; catalog number IS130D, lot number INS4957). The quantitative insulin-sensitivity check index (QUICKI) was also calculated as QUICKI = 1 / (log [insulin µU/ml] + log [glucose mg/dl]) (20). A QUICKI value < 0.35 was considered high IR, and a QUICKI value > 0.35 was considered low IR (20).

The study showed that 63.2% of the participants had high IR and 36.8% had low IR. Among participants with higher grades of AN (Grade 4 to 5), 62.5% had high IR, and 64.3% of those with high IR belonged to Grade 1 to 3 of AN (20). Patients with QUICKI < 0.357 tend to have a greater risk of IR, and they often present with symptoms of metabolic syndrome (20, 21).

Statistical analysis

Data were gathered and analyzed using R statistical software (version 3.6.3). The measures of continuous variables were expressed as mean, standard deviation, minimum, and maximum, and the categorical variables were presented in percentage/number format. Descriptive statistics and chi-squared / Fisher's exact test were utilized to assess the association between two categorical variables. A *p*-value of ≤ 0.05 was considered statistically significant.

Results

This study consisted of 87 AN patients, out of whom 52 (59.8%) were females and 35 (40.2%) were males (M:F = 2:3), with a mean age of 31.45 ± 8.82 years. The majority of the cases (93.1%) were younger than 45. A significant association was noted between AN and age (p = 0.009), but not with sex (p = 0.101). Table 1 shows the frequency distribution of various parameters. The neck was involved in almost all the patients and was the most common site involved (100.0%), indicating high sensitivity of neck lesions in identifying the presence of AN. This was followed by the axilla (60.9%) and knuckles (23.0%). Acrochordons were seen in 35.6% of the patients; 36.7% of the patients had only one site involved, and 63.3% had multiple sites manifesting AN lesions. Severity of neck lesions ranged from Grade 1 (1.1%) to Grade 4 (35.6%), with the AN grades showing a substantial positive association with

Table 1 | Frequency distribution of the various parameters.

Parameter		*n*	%
Age (years)	18–25	28	32.2
	26–35	25	28.7
	36–45	28	32.2
	46–55	4	4.6
	≥ 56	2	2.3
Sex	Female	52	59.8
	Male	35	40.2
Lesion site	Neck	87	100.0
	Axilla	53	60.9
	Knuckles	20	23.0
	Groin	13	14.9
	Antecubital fossa	8	9.2
Number of sites	1	32	36.7
	2	31	35.6
	3	11	12.6
	4	8	9.2
	5	5	5.7
Neck lesion severity grading	1	1	1.1
	2	27	31.0
	3	28	32.2
	4	31	35.6
Physical activity	High	50	57.5
	Low	37	42.5
Body mass index (kg/m²)	Normal (18.5–24.9)	10	11.4
	Overweight (25.5–29.9)	27	35.0
	Class 1 obesity (30.5–39.9)	17	19.5
	Class 2 obesity (35.5–39.9)	10	11.4
	Class 3 obesity (≥ 40)	23	26.4

BMI (p = 0.002) and WHR (p = 0.016). Interestingly, 83.9% of the cases were overweight or obese, and 42.5% had low physical activity.

High IR (< 0.35 QUICKI) was seen in 55 (63.2%) AN patients and low IR (> 0.36 QUICKI) in 32 (36.8%) AN cases. Tables 2 and 3 summarize the association of various parameters with AN severity and the number of AN lesion sites, respectively. IR, the QUICKI, and triglyceride levels showed no significant association with AN severity and the number of AN lesion sites (p > 0.05). However, LDL levels (p = 0.02) and WHR (p = 0.049) showed significant positive association with the number of AN lesion sites, but not with the severity grading (p > 0.05).

Discussion

This study examined the prevalence of IR among AN patients and assessed the association between IR and severity grades of AN. Patients with diabetes mellitus and polycystic ovary syndrome were excluded from this study because they are associated with both IR and AN, and hence could confound the results and override the significance of IR determination in AN patients (22).

An age distribution similar to this study was seen by Sadeghian et al. (41 ± 13.6 years) and Choudhary et al. (32.82 ± 10.19 years) (10, 23). Female preponderance was also reflected in the works of Kluczynik et al. (66%) (24). Predominance of AN lesions on the neck and axilla has also been noted in previous studies (1, 8). The presence of skin tags (35.6% in this study) was considered a sensitive indicator of impaired carbohydrate metabolism by Abbas et al. (25). The distribution of neck lesion severity approximated that observed by Shah et al. (26) for Grade 4 (30%), Grade 3 (24%), and Grade 2 (22%) lesions, but not Grade 1 (24%) lesions, which were much lower in this study. A close link between AN severity and obesity (BMI and WHR) has been validated by various researchers, such as Kluczynic et al. (p = 0.000) and Charnvises et al. (p = 0.001) (24, 27). This is because obesity is one of the principal causes of secondary IR because increased plasma levels of free fatty acids inhibit glucose transport activity (9). Hence, AN has been identified as an indicator of hyperinsulinemia with IR in obese people (9).

This study was unable to establish a relationship of IR with AN severity grades and the number of AN lesion sites, which is similar to the results of Charnvises et al., Hirschler et al., and Caceres et al., who concluded that AN could reflect obesity rather than representing an independent factor for IR because IR did not change in AN patients when compared to those without AN (27–29). This is in contrast to the studies by Gilkison and Stuart, Copeland et al., and Stuart et al., who found a significant strong correlation between AN and IR (p > 0.05) (8, 11, 12).

This study establishes that, although IR can be seen in some AN patients, its association with AN severity is not significant enough to qualify AN as a screening tool for IR. However, the association of obesity with both AN and IR justifies the role of weight-loss strategies and regular physical exercise in managing both AN and IR.

Nevertheless, this research has limitations in being single-centered with a limited sample size. These limitations can be overcome by multicentric, long-term, prospective studies with a larger sample size.

Conclusions

IR is present in AN patients, but the association between IR and AN severity is not significant enough to qualify AN as a screening tool for IR.

Table 2 | **Association of acanthosis nigricans neck lesion grading with various parameters.**

		Lesion grades		
Parameter		**1–3, *n* (%)**	**4–5, *n* (%)**	**Statistics**
IR (percentile)	‹ 25	2 (7.14)	3 (5.08)	
	25–75	4 (14.28)	6 (10.16)	$F = 0.5$, $df = 2$, $p = 0.77$
	› 75	22 (78.57)	60 (84.74)	
QUICKI IR	‹ 0.35 (high)	18 (64.28)	37 (62.71)	$x^2 = 0.02$, $df = 1$, $p = 0.88$
	› 0.36 (low)	10 (35.71)	22 (37.28)	
Triglyceride levels (mg/dl)	‹ 150	25 (89.28)	45 (76.27)	$F = 1.301$, $df = 1$, $p = 0.25$
	› 150	3 (10.71)	14 (23.72)	
LDL levels (mg/dl)	‹ 100	12 (42.85)	26 (44.06)	$x^2 = 0$, $df = 1$, $p = 0.99$
	› 100	16 (57.14)	33 (55.93)	
Waist/hip ratio	Normal	4 (14.28)	15 (25.42)	$x^2 = 0.8$, $df = 1$, $p = 0.36$
	Above normal	24 (85.71)	44 (74.57)	

x^2 = chi-squared, F = Fisher's value, IR = insulin resistance, LDL = low-density lipoprotein, QUICKI = quantitative insulin-sensitivity check index.

Table 3 | **Association of number of sites of acanthosis nigricans with various parameters.**

		No. of sites		
Parameter		**1–3, *n* (%)**	**4–5, *n* (%)**	**Statistics**
IR (percentile)	‹ 25	4 (5.40)	1 (7.69)	
	25–75	48 (10.81)	2 (15.38)	$F = 0.36$, $df = 2$, $p = 0.83$
	› 75	62 (83.78)	10 (76.92)	
QUICKI IR	‹ 0.35 (high)	46 (62.16)	9 (69.23)	$x^2 = 0.03$, $df = 1$, $p = 0.86$
	› 0.36 (low)	28 (37.83)	4 (30.76)	
Triglyceride levels (mg/dl)	‹ 150	61 (82.43)	9 (69.23)	$F = 0.52$, $df = 1$, $p = 0.46$
	› 150	13 (17.56)	4 (30.76)	
LDL levels (mg/dl)	‹ 100	28 (37.83)	10 (76.92)	$x^2 = 5.36$, $df = 1$, $p = 0.02$*
	› 100	46 (62.16)	3 (23.07)	
Waist/hip ratio	Normal	13 (17.56)	6 (46.15)	$F = 3.75$, $df = 1$, $p = 0.049$*
	Above normal	61 (82.43)	7 (53.84)	

x^2 = chi-squared, F = Fisher's value, IR = insulin resistance, LDL = low-density lipoprotein, QUICKI = quantitative insulin-sensitivity check index.
*Significant at 5% level of significance.

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