Original Article

Association of Acanthosis Nigricans and Insulin Resistance in Indian Children and Youth – A HOMA2-IR Based Cross-Sectional Study

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Abstract

Introduction: The American Diabetes Association includes acanthosis nigricans (AN) as an indicator of diabetes mellitus risk in overweight youth entering puberty. Some argue that AN is not an independent predictor of insulin resistance (IR), when body mass index (BMI) is controlled for. There is a paucity of studies on the association of AN and IR among children and young adults from India. Homeostatic model assessment-IR (HOMA2-IR), a computerized updated model, which is supposed to be superior to HOMA1-IR, has rarely been used for quantification of IR. **Methods:** Sixty cases (irrespective of BMI), aged 2–24 years with AN, and 30 age- and sex-matched normal weight controls were included. A thorough clinical examination and grading of AN was done. BMI, fasting glucose levels, and fasting insulin levels were measured for all. HOMA-IR calculator V.2.2.3 was used to calculate IR. Those with HOMA 2-IR >1.8 were considered insulin-resistant. Lifestyle modifications were advised for patients with IR. **Results:** The mean HOMA2-IR value in cases and controls was 2.422 and 1.322, respectively, which was statistically significant. Overweight and obese cases had 2.5 and 11.25 times higher risk of having IR, respectively, by logistic regression. The association of AN with IR was found to be statistically significant in normal weight cases when compared with controls (P = 0.045). Grade 4 of neck severity (P = 0.007), Grade 3 of neck texture (P = 0.001), and Grade 4 of axillary severity (P = 0.001) of AN were found to be significantly associated with IR. **Limitations:** The relatively small sample size may not reflect the accuracy of AN as a marker of IR. **Conclusion:** Acanthosis nigricans is associated with IR in both normal and obese. We propose that all children, adolescents, and youth with AN be screened for IR irrespective of BMI. Early identification and prompt lifestyle interventions may prevent or delay the onset of diabetes later.

Keywords: *Acanthosis nigricans, HOMA2-IR, insulin resistance*

Introduction

India is one of the epicenters of the global diabetes mellitus (DM) pandemic. It is estimated that there were 51 million diabetics in 2010, with a projected increase to 87 million by 2030.[1] Type 2 diabetes (T2D) among Indians has a younger age onset and is associated with greater abdominal obesity despite a relatively low body mass index (BMI), greater insulin resistance (IR), and early decline in beta cell function.[2] Obesity is one of the major risk factors for the development of DM and IR. Acanthosis nigricans (AN), initially coined by Unna in 1890, is characterized by thickened, hyperpigmented velvety plaques on the neck and intertriginous surfaces. The prevalence of AN varies from 7% to 74% in obese individuals.[3,4] Its incidence in pediatric population parallels the increase in childhood obesity and associated IR.[5] A systematic review found a pooled prevalence of childhood overweight and obesity in India to be 19.3%.[6] The American Diabetes Association includes AN as an indicator of DM risk in overweight youth entering puberty.[7] Some authors believe that AN is not an independent predictor of IR if BMI is controlled for.[8,9] We decided to study the association of AN and IR among children and youth (irrespective of BMI), as there is a lack of studies on this from India.

IR is considered as a common link in the development of disorders such as DM, metabolic syndrome (MS), and cardiovascular disease. Therefore, the association between IR and AN is of great interest to physicians. The Diabetes

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Prevention Program demonstrated that lifestyle interventions could prevent or postpone the onset of T2D by 58% in adults.[10] A measure of IR, which can predict IR and MS early, would have significant clinical utility. IR is measured by different methods such as hyperinsulinemic clamp and hyperglycemic clamp, intravenous glucose tolerance test, homeostatic model assessment-IR (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), McAuley's index (a triglyceride-based method), and oral glucose tolerance test. Glucose clamp method is the gold standard; however, it is cumbersome and time-consuming. HOMA-IR is a widely used and validated tool for quantifying IR in clinical and epidemiological studies.[11] The original model (HOMA1) was derived mathematically using the following formula:

HOMA1-IR = (FPI (mU/L) × FPG (mmol/L))/22.5

where FPI is the fasting plasma insulin and FPG is the fasting plasma glucose. Majority of studies on IR have used this formula. Subsequently, a computerized updated model (HOMA2-IR) was released. HOMA2-IR is an updated tool with corrections for peripheral and hepatic glucose resistance. We used HOMA2-IR to assess the association of AN and IR in children and youth.

Methods

A cross-sectional study was carried out from October 2013 to June 2015 after approval by the institutional ethical committee. All patients with AN between 2 and 24 years of age attending the dermatology outpatient department of our hospital were included in the study after consent. Children (<18 years) and youth (15–24 years) as per United Nations (UN) definition were taken up for the study.[12] The sampling technique used was purposive sampling. Known cases of DM were excluded. In all, 60 cases and 30 healthy age- and sex-matched controls were recruited. Patients with a known endocrinopathy and those with skin disorders that are known to be associated with MS (psoriasis, lichen planus, skin tags, etc.) were not taken as controls. A detailed history regarding onset, duration, and progression of skin lesions was taken. Five anatomical sites including the neck, axilla, groin, knuckles, elbows, and knees were assessed for the presence and severity of AN. For those with neck AN, texture was also measured. The quantitative scale by Burke was used to grade AN.[13] Other skin findings, if any, were noted.

Height was measured using a wall-mounted stadiometer with retractable measuring ruler (200 cm length) and weight using an analog mechanical weighing scale (min. grading 0.5 kg and maximum weight 125 kg). BMI was calculated using the following formula: weight in kilograms divided by height in meters square; classification was done according to World Health Organization (WHO) criteria. For adults, WHO defines overweight and obesity as BMI of greater than or equal to 25 and 30 kg/m^2, respectively. For those between 5 and 19 years, overweight is BMI-for-age greater than 1 standard deviation (SD) above the WHO Growth Reference median; and obesity is greater than 2 SD above the WHO Growth Reference median for weight.[14] For children between 2 and 5 years, weight for age more than 85th and 95th percentile as per WHO reference chart is defined as overweight and obese, respectively. Based on these criteria, the cases were divided into three groups – normal weight, overweight, and obese. Venous samples were collected from all cases and controls after 8 hours of fasting. Fasting glucose level [fasting blood sugar (FBS)] was measured by oxidase and peroxidase method. Fasting serum insulin (FSI) was measured by chemiluminescence using COBASe 601 fully automated immunoassay analyser (Roche Diagnostics, Switzerland). Glucose abnormalities were defined according to the criteria from WHO.[15] The normal reference range for serum insulin was 5–25 μIU/mL. HOMA-IR calculator V.2.2.3 was used to assess IR. Patients with HOMA 2-IR >1.8 were considered insulin-resistant,[16] and lifestyle modifications were advised to them.

Statistical analysis

Qualitative data is shown as proportions. Quantitative data is shown as mean ± SD. *T*-test and analysis of variance were done to analyze the difference between quantitative variables. Chi-square test was used to test the relationship between categorical variables. All analysis was done using SPSS software for Windows (V.20).

Results

Sixty cases and 30 age- and sex-matched controls were recruited. Females formed the majority [45 (75%)]; there were 15 males (25%). The mean age of cases was 17.27 ± 4.40 years and that of controls was 16.06 ± 4.89 years. More number of cases [52 (86.6%)] were between 13 and 24 years of age; 8 were between 0 and 12 years. In those with AN, 35% were of normal weight and 65% overweight or obese. The duration of AN varied from 3 months to 1 year. Fifteen patients had a positive family history of AN, of which eight were overweight or obese. Positive family history of DM was seen in 13 cases.

The mean FBS, FSI, and HOMA-IR values in cases and controls along with their comparisons are tabulated [Table 1]. FBS was found to be raised in one case and normal in all controls. Fasting insulin levels were raised in 14 cases and normal in controls (P = 0.000). A statistically significant difference was observed in mean insulin levels between male (25.4 ± 12.4) and female (17.3 ± 6.9 mIU/L) cases (P = 0.02). The mean serum insulin levels among normal, overweight, and obese cases with AN were found to be 15.63 ± 7.08, 18.78 ± 5.98, and 27.66 ± 12.85 mIU/L, respectively, whereas normal controls had a mean insulin of 10.17 ± 3.54 mIU/L.

The mean HOMA2-IR value in cases and controls was found to be 2.422 and 1.322, respectively. On evaluating

Table 1: Insulin levels, FBS, and HOMA-IR in cases and controls

Variables	Cases				Controls	Comparison between normal and obese cases of AN (*P*)	Comparison between normal weight cases and controls (*P*)
	Normal (*n*=21)	Overweight (*n*=28)	Obese (*n*=11)	Total	Normal weight (*n*=30)		
Fasting blood sugar (mg/dL), mean±SD	87.33±6.74	89.39±9.45	87.64±8.99	88.35±8.42	83.61±6.866	0.673	0.064
Serum insulin level (µIU/mL), mean±SD	15.63±7.08	18.78±5.98	27.66±12.85	19.30±8.91	10.17±3.54	**0.001**	0.001
HOMA2-IR, mean±SD	1.98±0.89	2.38±0.76	3.38±1.44	2.42±1.06	1.28±0.44	**0.001**	**0.001**
Insulin resistance (HOMA-IR >1.8), *n* (%)	6 (28.6%)	14 (50%)	9 (81.6%)	29 (49.3%)	3 (10%)	**0.016**	**0.045**

FBS=Fasting blood sugar; HOMA2-IR=Homeostatic model assessment-insulin resistance; SD=Standard deviation; Bold values are significant

HOMA2-IR values, it was observed that 29 (49.3%) cases (11 males and 18 females) and 3 (10%) controls showed IR, which was statistically significant ($P < 0.05$). It was found that 28.6% ($n = 6$) of normal weight cases, 50% ($n = 14$) of overweight, and 81.6% ($n = 9$) of cases with obesity had IR [Table 1]. By logistic regression method, overweight and obese cases had 2.5 and 11.25 times risk of having IR, respectively.

The FSI and HOMA2-IR values were significantly higher in obese compared to normal weight AN individuals ($P = 0.001$) [Table 1]. Similarly, a significant difference was observed between obese and overweight individuals with AN ($P = 0.08$ for FSI; $P = 0.014$ for HOMA2-IR). However, this difference was not statistically significant between normal and overweight cases of AN. The FSI, FBS, and HOMA2-IR values were significantly higher in normal weight cases ($P = 0.001$) compared to controls [Table 1]. IR was found in 28.6% of normal weight cases and 10% of normal weight controls, and this difference was statistically significant ($P = 0.045$).

Neck (90%, $n = 54$), axilla (80%, $n = 48$), and groin (58.3%, $n = 35$) were the common sites of involvement. All the three sites were involved in 51.7% of patients. Inframammary area (5.0%) and knuckles (3.3%) were rarely involved. Grade 3 and Grade 4 neck severity was seen in 18 (30%) and 12 (20%) cases, of which 61.1% and 83.3% cases had IR, respectively. Grade 3 neck texture was present in 14 (23.3%), and 12 (85.7%) of them showed IR. Grade 4 axillary severity was found in 12 (20%) cases, of which 11 (91.7%) had IR [Figure 1]. A significant association was observed with Grade 4 severity of neck ($P = 0.007$), Grade 3 texture of neck ($P = 0.001$), and Grade 4 severity of axillary AN and IR ($P = 0.001$) [Table 2]. No significant association was found between rarely involved sites and IR.

Associated cutaneous manifestations found in AN cases were skin tags in 28% ($n = 17$), followed by acne 11% ($n = 7$), dermatosis papulose nigra 3.3% ($n = 2$), and hirsutism in 5% ($n = 3$). A statistically significant association was seen between acne and IR (0.028). We did not find any association between a positive family history of DM or AN with IR.

Table 2: Grading of Acanthosis nigricans and its association with insulin resistance

	Insulin-resistant (*n*=29), *n* (%)	Noninsulin-resistant (*n*=31) *n* (%)	*P*-value *f*
Neck severity			
Grade 0	2 (6.9)	4 (12.9)	0.672
Grade 1	1 (3.4)	7 (22.6)	0.053
Grade 2	5 (17.2)	11 (35.5)	0.192
Grade 3	11 (37.9)	7 (22.6)	0.310
Grade 4	10 (34.5)	2 (6.5)	**0.007**
Neck texture			
Grade 0	2 (6.9)	5 (16.1)	0.426
Grade 1	2 (6.9)	9 (29.0)	0.060
Grade 2	13 (44.8)	15 (48.3)	0.986
Grade 3	12 (41.4)	2 (6.5)	**0.04**
Axillary severity			
Grade 0	5 (17.2)	7 (22.6)	0.846
Grade 1	2 (6.9)	6 (19.4)	0.299
Grade 2	4 (13.8)	12 (38.7)	0.059
Grade 3	7 (24.1)	5 (16.1)	0.651
Grade 4	11 (37.9)	1 (51.7)	**0.002**

f-ANOVA (Analysis of variance)-F test; Bold values are significant

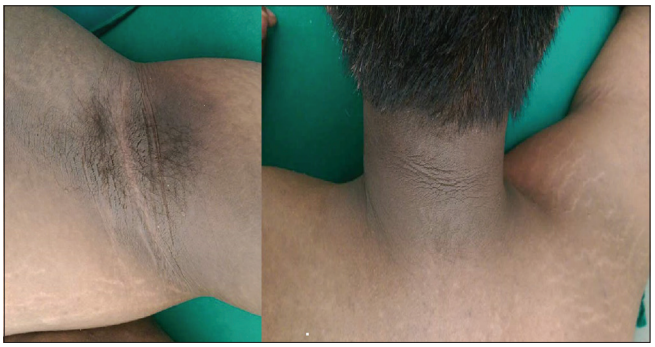

Figure 1: Grade 4 axillary and neck AN in an obese adolescent

Discussion

AN is characterized by symmetric, skin-colored or brownish, velvety lesions involving the neck, axillae, groin, inframammary folds, popliteal fossae, elbows, and umbilical region. It has been shown to be a strong predictor of IR in overweight and obese adults.[17] The accuracy of

AN as a cutaneous marker to predict IR in children and adolescents has not been well established.[9]

Several studies have shown AN to be more common in adolescent age group than in children.[18-20] Of the 60 cases recruited in our study, the maximum number of cases belonged to 13–18 years (43.3%) and 19–24 years (43.3%) age group. Adolescents were 2.47 times more likely to present with this dermatosis in a study on obese children and adolescents.[18] We included children (<18 years) and youth (15–24 years as per UN definition) as our study subjects[12] as this age group is amenable for lifestyle changes and dietary interventions.

The incidence of AN is equal in both men and women. There is no sex predilection.[4] We observed a male-to-female ratio of 1:2.5 in our study. A similar result was observed in a clinic-based study on AN patients, as also in a population-based study in India.[21,22] However, a higher male-to-female ratio has been found in previous studies conducted in obese children.[23] The female preponderance in our study might be due to increased cosmetic concern in them. The maximum duration of AN was 1 year, and history of onset of lesions during infancy was not present in any patient. A generalized distribution of AN lesions was not seen in normal weight AN cases. This helped us rule out generalized idiopathic benign AN, which presents as generalized AN (onset during infancy) and is not associated with obesity or systemic disease.[24]

The most common site involved was neck (90%), which has been found to be affected in more than 90% of cases of AN in several studies.[4,13,25] Gomez Flores *et al.*[26] observed knuckles to be commonly affected by AN in Latin American youth and suggested that it might indicate the likelihood of IR even in normal weight individuals. We did not find any significant association between knuckle involvement and IR. The racial difference in the study population (ours was Asian) might explain our observation.

Frank diabetes was not seen in any of our patients, similar to observations by others in obese children and adolescents.[9,18] This may be due to the younger age group of our study population. Fasting insulin was raised in 23.3% (n = 14) of cases. There was a highly significant association between the presence of AN and higher insulin levels (P = 0.000). Males with AN had higher insulin values than females (P = 0.02) in our study. A similar observation was made by Menon *et al.*[22] The mean insulin was 27.6 mIU/L/mL in obese cases. Studies in other parts of the world on obese children and adolescents with AN have found FSI to range from 15.4 to 31.4 mIU/L.[9,27,28] However, there are no Indian data on this. We observed a significant correlation between FBS and FSI in obese with AN (r = 0.422, P = 0.001). Aswani *et al.*[9] observed no correlation in both AN-negative and -positive obese children and proposed that AN was only a surrogate marker of IR. Guran *et al.*[23] found a correlation only in non-AN obese (r = 0.25), but not in AN group. They concluded that there is a disruption of insulin secretory dynamics in fasting state in AN cases. Levy-Marchal *et al.*, on the other hand, concluded in a consensus statement that there are no clear criteria for defining IR in children, and based on current criteria and methodology, there is no justification in screening them for IR with fasting insulin levels.[29]

HOMA-IR, which is developed for application in large epidemiologic investigations,[30] is an alternative to the glucose clamp and the most commonly used surrogate measure of IR *in vivo*. In terms of precision (reproducibility of measure), it is comparable to glucose clamp technique, but inferior to clamp technique in terms of accuracy. HOMA-IR makes it possible to study a large number of subjects and with a single glucose and insulin measurement in the fasting state.[31] Though HOMA1-IR has been widely used, HOMA2-IR gives a more accurate representation of the metabolic process because it models the feedback relationship between insulin and glucose in various organs.[11] Both HOMA-IR and HOMA2-IR are ethnic dependent and cut-off values cannot be uniformly used. The cut-off for HOMA1-IR ranges from 1.7 to 3.875 in nondiabetic adults across the world.[32] Studies evaluating HOMA-IR in obese children and adolescents are few, most of them outside India. Of these, a limited number are population-based studies, and the remaining have been conducted on small samples.[33] A systematic review has recommended a value of >2.5 HOMA1-IR as a cut-off in healthy adolescents of both genders to identify IR.[33] A similar observation was made in an Indian study.[34] A HOMA2-IR cut-off value of 1.8 and 1.67 has been proposed in two different studies in adults.[35,36] As HOMA2-IR-based studies are lacking, particularly among children and adolescents, we took a cut-off of 1.8, suggested by Gelonez *et al.* for our study.[35]

HOMA1-IR values ranging from 3.6 to 6 have been observed in studies on obese children and adolescents with AN from China, West Virginia, and Mexico,[9,19,28] while a value of 2.81 was found in a Portugal study.[37] We found a mean HOMA2-IR of 3.38 in obese children and youth with AN. Very few studies have compared the two HOMA-IR methods. A Brazilian study comparing both methods found that HOMA1-IR was higher than HOMA2-IR value.[35] A similar observation has been made by few others.[36,38] We did not calculate HOMA1-IR in our cases.

Among overweight and obese, IR was seen in 78.6% of cases (P = 0.038). Few studies in the past, comparing AN and non-AN obese adolescents using HOMA1-IR, found significantly higher IR in AN cases (43%–63%).[9,18,19,27] We did not have any overweight or obese as controls for comparison. A higher percentage of IR in obese and overweight was found in our study, as we have used HOMA2-IR, which has a lower cut-off than HOMA1-IR. Very few studies have assessed the role of AN as an independent marker of IR in obese, when weight was

controlled for. Nsiah-Kumi *et al.* observed that 82.4% of Native American children with AN had IR, but only 48.3% with IR had AN; they concluded that presence of AN alone is specific but not a sensitive tool for identifying IR in youth.[20] AN was found to be only a surrogate marker of IR in studies conducted in Bolivia and West Virginia.[8,9]

The mean serum insulin levels in normal weight AN cases and controls was 15.63 and 10.17, respectively. Puberty itself is associated with a decrease in insulin sensitivity, which recovers at completion of puberty. However, we did find a significant difference when values of normal weight cases were compared with that of age- and sex-matched controls.[39] Normal weight cases and controls had a mean HOMA2-IR of 1.98 and 1.3, respectively, in our study. The mean HOMA2-IR value in AN cases with a normal BMI (1.98) observed by us is higher than the HOMA1-IR value of 1.87 found in normal weight adolescents without AN by Garg *et al.*[40] However, HOMA2-IR values are expected to be lower than HOMA1-IR (based on previous observations).[35,36] This further strengthens the usefulness of AN as a marker of IR in individuals with a normal BMI. We could not find any studies assessing the utility of AN as a marker of IR in normal weight children and adolescents. A community-based cross-sectional survey in urban south Indian adult population has also concluded that AN was independently associated with increased risk of T2D.[41] A similar observation was made when diabetic cases were compared with controls.[25]

Skin tags were the most common skin condition observed in our cases (28%), similar to earlier studies.[42] Among patients with skin tags, 64.7% of patients showed IR; this, however, was not statistically significant ($P = 0.078$). But Valdés Rodríguez *et al.*[43] found that skin tags had a correlation with IR in children between 5 and 14 years of age. Acne was found in 11% of our patients and showed a significant association with IR (0.035). The higher incidence of acne might be because of the age group of our study population; we did not evaluate for acne severity and polycystic ovarian syndrome (PCOS) in our cases.

The grading of AN was done and its association with IR was assessed. Higher number of patients with Grade 3 and 4 severity of neck involvement had IR. A similar result was reported by Venkataswami *et al.*[44] We also found neck texture and axillary severity to be associated with IR. Grading of AN was not found to be useful in determining insulin sensitivity in overweight Hispanic children.[45] Posterolateral neck texture has been found to be an early sign of IR by Payne *et al.*[46] Neck but not axillary severity had a statistically significant correlation with IR values in adult diabetics.[47]

Limitations

The relatively small sample size may not reflect the accuracy of AN as a marker of IR in children and youth. HOMA-IR is not a gold standard test for measurement of IR. HOMA2-IR cut-off has been used from adult studies, as values for children and youth are not available.

Conclusion

A significant association of AN and IR was found both in normal weight and obese children and youth. The higher IR detection rate using HOMA2-IR in our study needs to be confirmed by further larger studies. IR was more common in those with higher grades of neck and axillary AN. Further large-scale population-based studies are necessary to evaluate the efficacy of AN as a marker of IR in children and youth.

We suggest that all children, adolescents, and youth with AN be screened for IR irrespective of their BMI.

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Conflicts of interest

There are no conflicts of interest.

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