Original Article

Acanthosis nigricans and its association with cardio-metabolic risk factors in children with overweight/obesity: A school-based cross-sectional study

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Abstract

Background: Acanthosis nigricans (AN) is a common finding often associated with hyperinsulinemia and childhood obesity. There has been a lack of studies evaluating the association of AN with underlying cardio-metabolic risk factors in children and adolescents. Our objective was to study the association between AN and cardio-metabolic risk factors in children with overweight/obesity. **Methods:** This cross-sectional study included school-going children (6–16 years of age) with overweight/obesity. Physical examination, anthropometry, and blood pressure (BP) data were collected. Fasting blood samples were collected to measure insulin, glucose, homeostasis model assessment index (HOMAIR), and lipid profile. **Results:** Of 1930 children screened, 545 had overweight/obesity, and were included. Boys to girls ratio was 1.27. AN was present in 46.4% of children. Children with AN had higher body mass index [BMI] ($P < 0.01$), waist circumference [WC] ($P < 0.01$), systolic ($P = 0.03$), and diastolic BP ($P = 0.02$), hyperglycemia ($P = 0.02$), hyperinsulinemia ($P < 0.01$), and a higher HOMA-IR ($P < 0.01$) compared to those without AN. HDL level was lower in children with AN. **Conclusions:** Children with overweight/obesity who have AN have significant elevations of BP, insulin level, and HOMA-IR. AN is a clinical marker that seems to be associated with cardio-metabolic risk factors in children with overweight/obesity in the given study population.

Keywords: Body mass index, HOMA-IR, insulin resistance, metabolic syndrome

Introduction

Childhood overweight and obesity can lead to the development of insulin resistance (IR), and metabolic syndrome (MS). These act as risk factors for the future development of type 2 DM (diabetes mellitus), and CVD (cardiovascular diseases) during early adulthood.[1] A study in India has found adolescents and young adults (14–25 years) with obesity to have a higher prevalence of IR.[2] This condition is considered a major physiological factor in the development of metabolic syndrome (MS), which is marked by elevated blood sugar levels, abnormal lipid profiles, and high blood pressure.[3] Clinical signs of IR include an increased WC (waist circumference) and the presence of AN (acanthosis nigricans). AN has been linked to hyperinsulinemia and childhood obesity. AN is most commonly seen around the neck (>90%) and in the axilla (73%) of the affected children.[4,5]

The Government of India initiated the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular

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Diseases, and Stroke (NPCDCS) in 2010 to address the growing incidence of NCDs (noncommunicable diseases). Subsequently, a health program targeted at adolescents aged 10–19 years, known as "Rashtriya Kishor Swasthya Karyakram (RKSK)", was also launched. India benefits from a robust network of trained healthcare workers deployed through the National Health Mission (NHM), enabling outreach even to the most remote areas. These personnel are equipped to identify conditions like acanthosis nigricans (AN) and refer cases to primary healthcare centers (PHCs) for further evaluation, counseling on lifestyle modifications, and appropriate management.

There has been a lack of studies on the association between AN and metabolic syndrome (cardio-metabolic risk factors) in children with overweight and obesity. The present study evaluated this association in school-going children.

Materials and Methods

This analytical observational (cross-sectional) study included school children of 6 to 16 years of age from Bhubaneswar, Odisha for one year (April 2017 to March 2018). Those with underlying DM, chronic diseases, or taking medications known to cause weight gain (overweight and obesity), or MS were excluded from the study. Enrollment of participants occurred following approval from the school authority and parental consent.

All the details (clinical and socio-demographic) were documented on CRFs (case record forms). General physical and systemic examinations were conducted to detect any abnormalities. Trained research staff performed measurements of various anthropometric parameters (weight, height, WC). Body mass index (BMI) was calculated by dividing weight (kg) by height (meter) and expressing it as kg/m^2. Weight (in gram [g]) was measured using a calibrated scale, and height (in centimeters [cm]) was measured using a stadiometer. WC (in cm) was measured in the mid-axillary line in a standing position (at the midpoint between the costal margin and iliac crest) with the help of a measuring (nonstretchable) tape. WC cut-offs were as per the published data in Indian children.[6] For blood pressure (BP) measurement, a standardized blood pressure (BP) measuring apparatus with appropriate-sized cuffs was used. Normal or abnormal BP (hypertension) recordings were classified as per the AAP (American Academy of Pediatrics) guideline.[7] BMI (kg/m^2) was interpreted as per the published data in Indian children.[8] IAP (Indian Academy of Pediatrics) classification was used for overweight and obesity (overweight - an adult BMI equivalent of 23, and obesity - an adult BMI equivalent of 27). AN was searched for in highly vulnerable areas like the neck, both axilla and skin folds. The pubertal staging was classified according to the standard criteria published previously.[9]

Blood samples in the fasting state were collected to measure the following parameters: glucose, insulin, and lipid profile (including triglycerides [TG], high-density lipoprotein [HDL], and low-density lipoprotein [LDL]). Deviations in the measured values of these parameters were defined according to the data published in Indian children.[10,11] Blood glucose was measured using the Glucose oxidase technique, and the lipid profile was analyzed with a Beckman Coulter AU5800 Clinical Chemistry Analyzer (California, USA). Insulin levels were also measured by a Siemens ADVIA Centaur XP Immunoassay System (Erlangen, Germany). We determined IR by the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) method, which is calculated as follows: fasting plasma insulin (mIU/L) multiplied by fasting plasma glucose (mmol/L), and divided by 22.5.[7,12] A HOMA- IR score of ≥2.5 indicates IR as defined previously in urban Indian adolescents.[13] The study was approved by the Institutional Ethics Committee (IEC) of AIIMS Bhubaneswar.

Sample size calculation

The sample size was calculated by using the cluster random sampling method, with schools serving as the clusters. The average prevalence of overweight/obesity among school-going children in Bhubaneswar is 28%.[14] The prevalence of MS in a previously published study in children overweight and obese is 20%, and in normal-weight children is 5.6%.[15] Consequently, the final sample size was calculated to be 2235, accounting for an absolute error of 2%, a fourfold increase due to the cluster design method, and a 10% attrition rate.

Statistical analysis

Statistical analysis was done by using the STATA 16.0 software (STATA Corporation, College Station, Texas, USA). Children were divided into two groups: Group A (AN present), and Group B (AN absent). To check the normal distribution of the data, the Kolmogorov–Smirnov test with Lilliefors correction was used. To check the homogeneity of inter-group variance, the Levene test was used. For inter-group comparisons, the Student's *t*-test (normally distributed and homogeneous data) and Mann–Whitney test (skewed data) were used. A chi-square test was employed to analyze the categorical variables. Pearson's correlation coefficient was utilized to explore the correlation between intra-group variables. A P value of <0.05 was considered statistically significant.

Results

After screening for eligibility, 1930 children were included, of which 28.2% (n = 545) were found to be overweight/obese. Metabolic syndrome (cardio-metabolic risk factors) was present in 119/545 children (point prevalence of 21.8%). Acanthosis nigricans (AN) were present in 253 of 545 (46.4%) children. Family history suggestive of DM and/or CVDs (cardiovascular diseases) was documented in 42.7%. The rate of exclusive breastfeeding was 68.1% at 6 months. Group A (AN present) constituted 51.8% (n = 131, boys =47), and Group B (AN absent) constituted 48.2% (n = 122, boys =55) of 253 children with AN. The two groups did not differ by the mean age of the children (P = 0.09), their gender (P = 0.12), and pubertal stage (P = 0.27) [Table 1]. However, there was a significant difference

Table 1: Characteristics of study children with and without acanthosis nigricans

Characteristics	Acanthosis nigricans (AN)		*P*-value
	Present (Group A=131)	Absent (Group B=122)	
Age (mean±SD)	11.5±2.8	10.4±3.0	0.09
Boys (*n*)	47	55	0.12
Puberty attended (*n*)	77	59	0.27
Anthropometric parameters			
BMI (kg/m^2) (mean±SD)	27.2±3.3	23.5±3.1	<0.01
BMI z-score (median, range)	2.4 (1.2–4.8)	1.76 (1.0-3.7)	<0.01
WC (cm) (mean±SD)	79.77±8.23	70.06±7.81	<0.01
WC z-score (median, range)	1.36 (1.02–2.01)	0.89 (0.63-1.15)	<0.01
Blood pressure (mmHg)			
SBP (mean±SD)	121.98±10.1	105.13±8.7	0.03
DBP (mean±SD)	80.29±3.6	71.24±1.9	0.02
Laboratory parameters (median, range)			
FPG (mg/dL)	92 (77–106)	79 (68–91)	0.02
TG (mg/dL)	98 (76-294)	82 (77–186)	0.27
HDL (mg/dL)	35 (27–44)	44 (26–48)	0.01
LDL (mg/dL)	103 (79–118)	99 (74–109)	0.45
Insulin (mIU/L)	16.5 (9.8–34.2)	9.7 (7.2–21.1)	<0.01
HOMA_IR	4.7 (0.9–22.5)	2.3 (0.4–7.1)	<0.01

BMI: Body mass index, WC: Waist circumference, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, FPG: Fasting plasma glucose (normal range: 70–110 mg/dl), TG: Triglyceride (normal range: 27–185 mg/dl), HDL: High-density lipoprotein (normal range: 12–86 mg/dl), LDL: Low-density lipoprotein (normal range: 32–202 mg/dl), FPI: Fasting plasma insulin (normal range: 3–8 mIU/mL)

in the anthropometric parameters between the two groups: BMI ($P < 0.01$), BMI z-score ($P < 0.01$), WC ($P < 0.01$), WC z-score ($P < 0.01$) confirming that AN was associated with a higher adiposity index [Table 1].

On analyzing the blood pressure (BP) values, significantly higher values for systolic ($P = 0.03$), and diastolic ($P = 0.02$) BP was noted in children with AN (Group A). Except for HDL level (significantly lower in Group A, $P = 0.01$), there was no significant difference in the levels of TG and LDL [Table 1]. In Group A, plasma glucose ($P = 0.02$), plasma insulin ($P < 0.01$), and HOMA-IR index were significantly higher without a diagnosis of DM [Table 1]. HOMA-IR was deranged in 55.1% of participants (Group A) and 34.4% of participants (Group B), respectively. The basal insulin level was 9.8–34.2 mUI/mL (Group A), and 7.2–21.1 mUI/mL (Group B), respectively. In Group A, the basal plasma insulin level was >15 mUI/mL in 52.4% of cases (32.6% of children in Group B). The correlation coefficients of various parameters in the 2 groups are shown in Tables 2 and 3. In Group A, a significant positive correlation was noted between TG levels, and anthropometric parameters like BMI and WC [Table 2]. In Group A, a significant positive correlation between plasma insulin level and HOMA-IR was noted with BP and TG levels, and a significant negative correlation was noted with HDL level [Table 3].

Table 2: Simple linear correlation* between BMI and waist circumference with clinical and laboratory parameters in those with and without acanthosis nigricans

Characteristics	BMI				Waist circumference (WC)			
	With AN		Without AN		With AN		Without AN	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
BMI	-	-	-	-	0.85	0.0	0.89	0.0
BM z-score	0.62	0.0	0.56	0.0	0.51	0.0	0.49	0.0
WC	0.85	0.0	0.89	0.0	-	-	-	-
WC z-score	0.63	0.0	0.54	0.0	0.50	0.0	0.48	0.0
SBP	0.43	0.0	0.54	0.0	0.48	0.0	0.53	0.0
DBP	0.37	0.0	0.42	0.0	0.36	0.0	0.44	0.0
HDL	−0.12	0.28	−0.02	0.76	−0.14	0.22	-0.07	0.44
LDL	0.17	0.15	0.03	0.67	0.31	0.0	0.04	0.71
TG	0.24	0.02	0.11	0.29	0.27	0.01	0.15	0.22
FPG	0.62	0.05	0.12	0.31	0.09	0.42	0.14	0.28
Insulin	0.48	0.0	0.45	0.0	0.46	0.0	0.42	0.0
HOMA-IR	0.46	0.0	0.46	0.0	0.47	0.0	0.45	0.0

*Pearson's correlation

Discussion

In the current study, children in Group A (AN present) exhibited higher BMI (including BMI z-scores), WC (including WC z-scores), BP, insulin levels, and HOMA-IR values, along with lower HDL levels. Additionally, a correlation was found between plasma insulin, HOMA-IR, and BP measurements. A previous Indian study reported a 21.8% prevalence of various metabolic syndrome (MS) components among school-aged children and adolescents.[16] In that study, the frequency of MS components was as follows: WC (most common), HDL level, TG level, BP, and plasma glucose (least common). Another study on prepubertal children (aged 2–11 years) who were obese or overweight found a 27.9% prevalence of AN with 61.4% cases associated with increased abdominal circumference (AC), 55.7% associated with low HDL level, and 16.4% cases diagnosed with MS.[17] Similarly, another study including children with overweight/obesity found 51.5% of children with AN had significant increase in BP measurements and AC, and deranged laboratory parameters suggesting an association between AN and MS.[18] A study from South India involving 165 children reported similar findings.[19] In our study, 46.4% of children had

Table 3: Simple linear correlation* between HOMA-IR and insulin with clinical and laboratory parameters in those with and without acanthosis nigricans

Characteristics	HOMA-IR				Insulin			
	With AN		Without AN		With AN		Without AN	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
BMI	0.46	0.0	0.46	0.0	0.48	0.0	0.45	0.0
BM z-score	0.23	0.0	0.28	0.0	0.22	0.0	0.20	0.0
WC	0.47	0.0	0.45	0.0	0.46	0.0	0.44	0.0
WC z-score	0.25	0.0	0.25	0.0	0.26	0.0	0.24	0.0
SBP	0.31	0.0	0.12	0.25	0.34	0.0	0.16	0.17
DBP	0.23	0.02	-0.04	0.69	0.32	0.0	0.03	0.09
HDL	-0.24	0.01	-0.07	0.45	-0.22	0.03	-0.13	0.27
LDL	0.16	0.17	0.07	0.42	0.11	0.34	-0.03	0.78
TG	0.32	0.0	0.13	0.28	0.31	0.0	0.16	0.17
FPG	0.62	0.05	0.12	0.31	0.09	0.42	0.14	0.28
Insulin	0.95	0.0	0.92	0.0	-	-	-	-
HOMA-IR	-	-	-	-	0.95	0.0	0.92	0.0

*Pearson's correlation

AN, showing similar changes in BP, WC, and laboratory results (lipid profile, FPG, insulin, and HOMA-IR).

One study involving 194 children aged 2–18 years found a significant association between AN and higher values of BMI, AC, plasma insulin level, and HOMA-IR.[5] It also noted that AN was significantly more prevalent in individuals with non-white skin color (5.4 times higher compared to white skin). Another study involving 160 children with obesity found that 41.8% had AN and reported similar levels (no significant difference) of hyperglycemia, hyperlipidemia, HDL level, LDL level, BP, insulin, and HOMA-IR between those with and without AN.[4] A large study (6,328 individuals were included) found that those who were overweight during childhood had a higher risk of developing hypertension during adulthood.[20] A positive association between AN and increased BP suggests that AN should be considered a warning sign for early cardiovascular alterations, which implies a need for early intervention in pediatric patients. Insulin resistance, characterized by a suboptimal biological response to serum insulin levels, leads to hyperinsulinism as the body attempts to compensate.[21] An increase in adiposity during childhood is the likely triggering event that disrupts the metabolism of glucose in the body giving rise to IR (insulin resistance). Consequently, the markers (both clinical and laboratory) of IR should be closely monitored in children with overweight/obesity.[16] A positive correlation was found between insulin, HOMA-IR, anthropometric parameters, and TG levels. Similar findings from other studies support our results,[22,23] showing that IR is associated with an increased risk of cardio-metabolic disorders in adulthood. However, it should be noted that, while fasting plasma insulin levels and HOMA-IR are used as markers of IR in epidemiological studies, they are not recommended as routine screening tests in clinical practice for assessing children with overweight/obesity.[21] Clinical markers such as AN are particularly important, as they may indicate the need for preventive strategies.

Insulin resistance (IR) often precedes diabetes by approximately 10–15 years, and AN is a reliable marker of IR.[24] Consequently, AN has been proposed as a simple, noninvasive, cost-effective tool for detecting prediabetes, DM, and MS.[24] The American Diabetes Association (ADA) includes AN as an indicator of DM risk in overweight adolescents entering puberty. Given the higher risk for noncommunicable diseases (NCDs) in Indians, early detection of AN as a marker of IR is critically important.[24] However, AN remains an underutilized practical tool. Primary care physicians can play a crucial role in identifying AN and referring affected children for further evaluation and lifestyle interventions, which could help in the large-scale prevention of NCDs in the future.

Our study has several limitations: (i) as a cross-sectional study, it does not establish causality, (ii) we did not perform an oral glucose tolerance test (OGTT) to assess impaired glucose tolerance (IGT) or type 2 DM, and (iii) we did not collect data on physical activity and dietary patterns.

Conclusions

In the current study, children with overweight/obesity who have AN have significant elevations of BP, insulin, and HOMA-IR. AN is a clinical marker that is shown to be associated with MS or cardio-metabolic risk factors in children with overweight/obesity.

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Conflicts of interest

There are no conflicts of interest.

References

1. Tharkar S, Devarajan A, Kumpatla S, Muthukumaran P, Viswanathan V. Insulin resistance and cardio metabolic abnormalities among overweight South Indian children: Chennai slim and fit programme. Indian J Community Med 2013;38:121-2.
2. Misra A, Vikram NK, Arya S, Pandey RM, Dhingra V, Chatterjee A, *et al.* High prevalence of insulin resistance in postpubertal Asian Indian children is associated with adverse truncal body fat patterning, abdominal adiposity and excess body fat. Int J Obes Relat Metab Disord 2004;28:1217-26.
3. Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Metabolic syndrome in South Asians. Indian J Endocrinol Metab 2012;16:44-55.
4. Maguolo A, Maffeis C. Acanthosis nigricans in childhood: A cutaneous marker that should not be underestimated, especially in obese children. Acta Paediatr 2020;109:481-7.
5. Kluczynik CE, Souza LC, Albuquerque FC, Mariz LS, Solano GB, Medeiros CC. Acanthosis nigricans and insulin resistance in overweight children and adolescents. An Bras Dermatol 2012;87:531-7.
6. Khadilkar A, Ekbote V, Chiplonkar S, Khadilkar V, Kajale N, Kulkarni S, *et al.* Waist circumference percentiles in 2-18 year old Indian children. J Pediatr 2014;164:1358-62.
7. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, *et al.* Subcommittee on screening and management of high blood pressure in children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140:e20171904. doi: 10.1542/peds.2017-1904.
8. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, Agrawal KK, Agrawal KK, Tamboli S, Banerjee M, *et al.* Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Indian Pediatr 2015;52:47-55.
9. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170-9.
10. Jain V, Kumar A, Agarwala A, Vikram N, Ramakrishnan L. Adiponectin, interleukin-6 and high-sensitivity C-reactive protein levels in overweight/obese Indian children. Indian Pediatr 2017;54:848-50.
11. Marwaha RK, Khadgawat R, Tandon N, Kanwar R, Narang A, Sastry A, *et al.* Reference intervals of serum lipid profile in healthy Indian school children and adolescents. Clin Biochem 2011;44:760-6.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
13. Singh Y, Garg MK, Tandon N, Marwaha RK. A study of insulin resistance by HOMA- IR and its cut-off value to identify metabolic syndrome in urban Indian adolescents. J Clin Res Pediatr Endocrinol 2013;5:245-51.
14. Patnaik L, Pattanaik S, Sahu T, Rao EV. Overweight and obesity among adolescents, a comparative study between government and private schools. Indian Pediatr 2015;52:779-81.
15. Friend A, Craig L, Turner S. The prevalence of metabolic syndrome in children: A systematic review of the literature. Metab Syndr Relat Disord 2013;11:71-80.
16. Das RR, Mangaraj M, Panigrahi SK, Satapathy AK, Mahapatro S, Ray PS. Metabolic syndrome and insulin resistance in schoolchildren from a developing country. Front Nutr 2020;7:31.
17. Madeira IR, Carvalho CN, Gazolla FM, Matos HJ, Borges MA, Bordallo MA. Cut-off point for homeostatic model assessment for insulin resistance (HOMA-IR) index established from receiver operating characteristic (ROC) curve in the detection of metabolic syndrome in overweight pre-pubertal children. Arq Bras Endocrinol Metab 2008;52:1466-73.
18. Palhares HMDC, Zaidan PC, Dib FCM, Silva APD, Resende DCS, Borges MF. Association between acanthosis nigricans and other cardiometabolic risk factors in children and adolescents with overweight and obesity. Rev Paul Pediatr 2018;36:301- 8.
19. Thiagarajan S, Arun Babu T, Manivel P. Acanthosis nigricans and metabolic risk factors in obese children. Indian J Pediatr 2020;87:162.
20. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, *et al.* Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
21. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, *et al.* Insulin resistance in children: Consensus, perspective, and future directions. J Clin Endocrinol Metab 2010;95:5189-98.
22. Romualdo MC, Nóbrega FJ, Escrivão MA. Insulin resistance in obese children and adolescents. J Pediatr (Rio J) 2014;90:600-7.
23. Mieldazis SF, Azzlis LA, Junqueira VB, Souza FI, Sarni RO, Fonseca FL. Hyperinsulinism assessment in a sample of perpubescent children. J Pediatr (Rio J) 2010;86:245-9.
24. Tyebkhan G, Velaskar S, Yadav P, Phiske M, Shah D. An Indian expert group review of acanthosis nigricans with recommendations for early detection and timely management. J Assoc Physicians India 2024;72:74-84.