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Association Of Acanthosis Nigricans With Deranged Lipid Profile Among Obese Pediatric Population

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Abstract
Objective: *To evaluate the presence or absence of Acanthosis Nigricans and its association with metabolic alterations in a group of obese and overweight children.*
Methods: *A cross-sectional study of 102 overweight school going children in Panipat, based on body mass index of the age group of 9-13 yrs, divided into two groups, presence of Acanthosis nigricans (case group) or absence (control group). Several metabolic indices such as serum concentrations of total cholesterol, HDL cholesterol, triglycerides, uric acid, gamma GT and fasting glucose were measured by the enzymatic colorimetric method to find an association of Acanthosis nigricans and metabolic changes.*
Results: *The Acanthosis nigricans group represented 51.5% of the sample. The mean age was similar between two groups. The group with Acanthosis nigricans presented higher body mass index, body mass index ($p<0.0001$). There was no significant difference in the analysis of lipid profile, except for the high-density cholesterol, which was lower ($p=0.003$) in the group with acanthosis. On the other hand, uric acid ($p<0.0001$), fasting glycemia ($p=0.006$) were significantly higher in the group with Acanthosis nigricans.*
Conclusions: *The present study highlights the high prevalence (51.5%) of Acanthosis nigricans in overweight and obese children, and its association with a major risk factors for cardiovascular disease, that is dyslipidemia. This suggests that it can be a useful practice to evaluate patients of acanthosis nigricans for dyslipidemia as a preventative measure. Such measures would represent an improvement in the medical attention and quality of life for children and decrease the chances of developing serious disorders in future.*
Keywords: *Acanthosis nigricans; Pediatric obesity; Insulin resistance; Risk factors.*

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I. Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). For Children aged between 5–19 years Overweight and obesity are defined as based on body mass index (BMI), shown in Table 1.

Table 1: Definitions are the ones used by the World Health Organisation

	Children
Overweight	BMI >1 standard deviation above the WHO reference median
Obese	BMI >2 standard deviations above the WHO reference median

Childhood obesity is a chronic disease with multifactorial etiology which is becoming increasingly prevalent.[1] This high prevalence of childhood obesity is considered as a major risk factors for cardiovascular diseases. Childhood obesity is one of the gravest public health problems of the 21st century, having become an emerging global epidemic that implies immediate and long-term effects. One such dermatological change often associated with obesity is AN. The increased incidence of which runs parallel with that of obesity. Acanthosis nigricans is a velvety, darkening of the skin that usually occurs in intertriginous areas. This hyperpigmentation has poorly defined borders, usually occurs in skin fold areas, such as the back of the neck, axilla, and groin, and may include thickening of the skin. In children, the most common site of acanthosis nigricans is the posterior neck.[5]

Acanthosis nigricans may at first come out to be just a dermatological problem but in reality is deeply associated with metabolic changes, sometimes spanning to a constellation of problems together bundled as metabolic syndrome. Metabolic syndrome is defined as a group of disorders that includes, in addition to obesity, insulin resistance — playing a central role in its development — dyslipidemia, arterial hypertension and other metabolic disorders associated with cardiovascular disease.[4][3] Table 2 shows the total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride distribution.

Table 2: T Chol, HDL Chol, LDL Chol and TG distribution according to age group and sex (mg/dl)		
	7-10 years	10-12 Years
1.Total Cholesterol		
(Male)	145.1 ± 25.38	158.7 ± 21.23
(Female)	156.4 ± 27.82	161.6 ± 23.09
2. S. HDL		
(Male)	53.5 ± 7.03	60.7 ± 11.70
(Female)	61.0 ± 11.77	66.7 ± 8.75
3. S.LDL		
(Male)	76.4 ± 20.30	80.3 ± 19.26
(Female)	75.3 ± 24.60	75.8 ± 20.26
4. S. Triglycerides		
(Male)	84.0 ± 15.92	86.7 ± 28.80
(Female)	98.5 ± 54.41	93.2 ± 44.09

Worldwide, the prevalence of obesity among children and adolescents aged 5 to 19 years has worsened by 6% from 0.8% [0.6% - 1.1%] in 1975 to 6.8% [6.1% - 7.6%] in 2016.

The rising prevalence of obesity is expected to be steepest among children and adolescents, rising from 10% to 20% of the world's boys during the period 2020 to 2035, and rising from 8% to 18% of the world's girls. [2]

There are multiple factors involved in the development of acanthosis nigricans including Familial AN, Obesity associated, Medications like glucocorticoid associated, Endocrine associated like Insulin resistance, Malignancy like lymphoma associated or autoimmune. [6]

The aim of the present study is to obviate whether, in a group of school children, AN is associated with the Z-score of the body mass index (BMI) and dyslipidemia.

II. Aims And Objectives

AIM

To establish the presence or absence of Acanthosis nigricans and its association with metabolic alterations in a group of obese and overweight children and adolescents.

Objective

To establish an association of Acanthosis nigricans with unfavorable changes in lipid profile, often linked as a cardio-metabolic risk factors in overweight and obese children, consolidating a relation between BMI and presence of Acanthosis nigricans in young children.

III. Material And Methods

A cross sectional study conducted among 174 overweight/obese children of the age group of 9-13 years from public school in Panipat who were divided into two groups, according to presence of Acanthosis nigricans (case group) or absence (control group).

STUDY SITE: Department of Pediatrics, NC Medical College and Hospital, Panipat, Haryana

STUDY PERIOD: sample was collected in a single visit and study was carried over a period of 6 months.

SAMPLE SIZE: 174 individuals participated and after exclusion by chronic diseases (3 individual), not agreed participation (10 individuals) and refusal for investigations (59) the final sample size constituted of 102 children with overweight and obesity.

INCLUSION CRITERIA: Children of the age group 9-13 yrs with Z score of BMI >+1 and >+2 will be included in this study

EXCLUSION CRITERIA:

1. Children with history of any chronic illness

2. Children on any long term medications like glucocorticoids or insulin
3. Children with ongoing illness.

Methodology

This study was conducted in which all the children of the age group 9-13 years studying in a private school of Panipat were screened, based on Body Mass Index (BMI) according to WHO Guidelines, 174 individuals participated and after exclusion by chronic diseases (3 individual), not agreed to participation (10 individuals) and refusal for investigations (59), the final sample constituted of 102 children with obesity. Children were weighed on a platform-type digital electronic scale with capacity of up to 150 kg and 100-g precision. The subjects were wearing light clothing, barefoot, positioned vertically in the center of the scale, and standing still.

Height was measured in upright position, feet united in parallel, barefoot, on a wall stadiometer, graduated up to 220 cm and divided in millimeters. The height was measured three times in a row, with average considered as the final result.

Body mass index (BMI) was calculated dividing weight (kg) by squared height (m^2) (kg/m^2). Individuals were categorized as overweight (+1≥ Z score of BMI <+2) and obese (Z score of BMI ≥+2).

Physical examination consisted of a detailed evaluation of the skin in search of clinical signs of insulin resistance, which is evidenced by the presence of AN, visually assessed in the neck, axilla, elbows, and inguinal region.

Children were then divided into two groups according to presence of Acanthosis nigricans or absence: Group 1 (G1), with 52 children with AN, and Group 2 (G2), with 50 children without AN.

The children falling in the inclusion criteria were called for further investigation to NC Medical College, Israna, Panipat. Informed consent was taken from the parent/tutor with informed approval of the participating child for further investigations.

After a fast of 12 hours, with previous asepsis, blood samples were taken by venipuncture with the system of a Vacutainer vacuum. The tubes with blood were centrifuged for 10 min at 3,500 rpm to obtain serum. In these serum samples, the concentration of triglycerides (mg/dL) and cholesterol (mg/dL) was quantified with colorimetric enzymatic methods.

Serum concentrations of total cholesterol, HDL, LDL, triglycerides, uric acid, gamma GT and fasting were measured by the enzymatic calorimetric method.[7]

In comparisons between groups, the Student-t test was used when data had normal variance distribution and homogeneity. For comparison or association between categorical variables, the chi-square test was used.

IV. Results

Group 1 (with AN, n=52) was composed of 17 males and 35 females, representing 50.9% of the total sample, and Group 2 (without AN, n=50) represented 49% of the total sample with 19 males and 31 females. Mean age was similar between groups (p=0.70); gender and pubertal stage (p=0.34 and p=0.50, respectively) were also not statistically significant in comparison. These clinical and laboratory data are listed in Table 1.

Table 1: Clinical and laboratory categorization of groups with and without Acanthosis nigricans

	Presence of Acanthosis (n=52)	Absence of Acanthosis (n=50)	P value
Age (in years)$_a$	11.7 ± 2.9	10.8 ± 3.1	0.07
Gender (male/female)$_b$	17/35	19/31	0.34
BMI (kg/m^2)$_a$	27.4 ± 3.4	23.4 ± 3.6	<0.0001
Z-BMI $_c$	2.5 (1.2-4.9)	1.88 (1.0-3.9)	<0.0001
Total cholesterol (mg/dl) $_c$	164.3 (88.7-230.5)	158.9 (103.5-279.4)	0.87
HDL – cholesterol (mg/dl) $_a$	43.0 ± 10.7	48.1 ± 10.8	0.003
LDL- cholesterol (mg/dl) $_a$	102.8 ± 28.4	99.4 ± 32.5	0.48
Triglycerides (mg/dl) $_c$	86.0 (41.0-286.0)	83.0 (31.0-445.0)	0.28
Fasting glycemia (mg/dl) $_a$	89.2 ± 10.5	84.1 ± 12.5	0.006
Gamma GT (U/L) $_c$	19.3 (0.2-55.9)	14.8 (5.7-38.0)	<0.0001
Uric acid (mg/dl)	4.9 ± 1.0	4.2 ± 1.0	<0.0001

BMI: body mass index; Z-BMI: body mass index score; TG/HDL-c: relation triglycerides/HDL-cholesterol; Gamma GT: Gamma-glutamyltransferase; (a) Students' t test: values expressed in mean ± standard deviation; (b) chi-square test; (c) Mann-Whitney test: values expressed median (Vmin.–Vmax.).

Statistical analysis of anthropometric data showed a significant difference between G1 and G2 as to BMI (p<0.0001) and Z score of BMI (p<0.0001), confirming that patients with AN had higher BMI.

Regarding laboratory data, groups were not statistically different when it came to lipid profile, except for HDL cholesterol, with lower mean in G1 compared to G2 (p=0.003) (Table 1).Serum concentrations of uric acid (p<0.0001) and GPT (p<0.0001) were significantly higher in G1.(Table 1).

Fasting glycemia was significantly higher in G1 when compared to G2. Correlations between clinical and laboratorial data of G1 and G2 are shown in Tables 2 and 3. There was a significant positive association of BMI with triglycerides in G1 only (Table 2). The analysis of correlation of triglycerides was also significant in G1 only, as well as the negative correlation with HDL cholesterol.

Table 2: Simple linear correlation between body mass index with clinical and laboratory parameters in the groups of overweight and obese children with and without acanthosis.

BMI				
	With AN		Without AN	
	r	**P value**	**R**	**P value**
Z-BMI	**0.60**	**0.00**	**0.55**	**0.00**
Total cholesterol	**0.20**	**0.06**	**0.01**	**0.92**
HDL-cholesterol	**-0.11**	**0.29**	**-0.02**	**0.82**
LDL-cholesterol	**0.16**	**0.14**	**0.04**	**0.72**
Triglycerides	**0.25**	**0.02**	**0.10**	**0.34**
Fasting glycemia	**0.63**	**0.05**	**0.11**	**0.33**
Gamma GT	**0.25**	**0.02**	**0.18**	**0.14**
Uric Acid	**0.40**	**0.00**	**0.46**	**0.00**

V. Discussion

Obesity is a public health problem considered to be a worldwide epidemic. Acanthosis Nigricans is now frequently found in children and adolescents, especially in populations with a high prevalence of obesity, insulin resistance and DM-2. The present study explored the possible association of AN with obesity, as well as the possibility of using AN as an early non-invasive marker of metabolic disorders widely related to identify obesity in school children so that plausible interventions can be made to prevent cardiovascular sequelae in overweight and obese children[8,9].

The incidence of AN in children has increased together with that of obesity and insulin resistance. For this reason, the American Diabetes Association has recommended the early detection of AN as a criterion for identifying children at risk for developing DM-2. In a study conducted with pre pubertal children with obesity or overweight aged 2 to 11 years old, Madeira et al.[10] reported 27.9% of the sample with AN, 61.4% with increased AC, 55.7% with low HDL cholesterol, and 16.4% of subjects meeting the criteria for metabolic syndrome diagnosis. Meanwhile, Mukhtar et al. documented an 18.9% prevalence of AN in obese adolescents in New Mexico[11], Nguyen et al. reported 25% of AN in overweight Afro-American children[12], and Stuart et al. found 38% of AN in Native Americans[13]. On the other hand, Thivel D and Maisonneuve B have reported the prevalence of AN to be as high as 68 in obese children[14]. These differences in prevalence of AN have been related to the proportion of overweight and obesity in the groups under study.

In our study, we evaluated changes that would be associated with the presence of AN in children with obesity and overweight. The group with AN (G1) had higher BMI, Z score of BMI, fasting glycemia, gamma GT and uric acid values, but lower HDL cholesterol values.

In addition, Klucznik et al[15] assessed 194 children and adolescents between the ages of 2 and 18 years and showed an association between AN and BMI

In our study, 51.5% of the patients with AN and a tendency to more significant changes in BMI and laboratory tests, indicating that AN is associated with metabolic syndrome in overweight and obese children. We also found a statistically significant difference as to fasting glycemia (higher in the group with AN) and HDL cholesterol (lower in the group with AN). One can conclude that AN is a clinical finding that is strongly associated with metabolic alterations, insulin resistance, hyper-insulinemia, obesity and metabolic syndrome.

One of the limitations of the present study is that the data do not come from a representative sample of all children of primary schools of Panipat. Nonetheless, the sample is made up of a homogeneous population in a certain age group.

VI. Conclusion

In summary, the results of the present study highlight the high prevalence (51.5%) of AN in overweight and obese children, and its association with two risk factors for cardiovascular disease, the distribution of body fat and dyslipidemia. It is suggestive that early re cognition of relation between acanthosis nigricans and metabolic disorder can be preventative intervention in high risk children who might later develop cardiovascular disease, DM-2 and other metabolic disorders.

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