Acanthosis nigricans and insulin resistance in overweight children and adolescents *

Acantose nigricans e resistência insulínica em crianças e adolescentes com excesso de peso

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Abstract: BACKGROUND: Studies have suggested an association between the presence of acanthosis nigricans (AN) and the development of diabetes.
OBJECTIVE: To investigate the association between AN and insulin resistance (IR) in overweight children and adolescents receiving care at the Center for Childhood Obesity, Campina Grande, PB.
METHODS: This cross-sectional study was conducted between April 2009 and April 2010 including 194 individuals of 2 to 18 years of age receiving care within the Brazilian national health network. The presence of acanthosis nigricans was verified and anthropometric measurements were taken. The following tests were performed: insulin, triglycerides, HDL-cholesterol, glucose and homeostasis model of assessment - insulin resistance (HOMA-IR). Statistical analyses were performed using the SPSS software program, version 17.0.
RESULTS: There was a greater prevalence of females (66%), brown-skinned individuals (63.4%), adolescents (61.3%) and severely obese individuals (66.5%). Acanthosis nigricans was identified in 58.2% and IR in 42.7% of the participants. Acanthosis nigricans was associated with being non-white (p = 0.003), with being an adolescent (p = 0.003) and with IR (p = 0.001). Non-white individuals, adolescents and those with insulin resistance were 5.4, 2.47 and 2.66 times more likely to have acanthosis nigricans, respectively.
CONCLUSION: The results of this study indicate a need to train healthcare professionals to identify acanthosis nigricans, since this condition is associated with IR. Identifying acanthosis nigricans in childhood permits the safe and timely treatment of cardiometabolic disorders through careful monitoring and appropriate treatment.
Keywords: Acanthosis Nigricans; Adolescent; Child; Insulin Resistance

Resumo: FUNDAMENTOS: Estudos sugerem haver associação entre a presença de Acantose Nigricans e o desenvolvimento do diabetes.
OBJETIVO: Verificar a associação entre Acantose Nigricans e Resistência Insulínica (RI) em crianças e adolescentes com excesso de peso, atendidos no Centro de Obesidade Infantil, Campina Grande-PB.
MÉTODOS: Estudo transversal realizado entre abril/2009 a abril/2010, com amostra de 194 pessoas entre 2 e 18 anos, usuários do Sistema Único de Saúde. Na avaliação, foi observada a presença de AN e verificadas as medidas antropométricas. Foram realizados os exames: insulina, triglicerídeos, HDL-colesterol, glicose e HOMA-IR. As análises estatísticas foram realizadas no SPSS, 17.0.
RESULTADOS: Houve maior prevalência do sexo feminino (66%), pardos (63,4%), adolescentes (61,3%) e obesos graves (66,5%). Foi identificada AN em 58,2% e RI em 42,7%. A Acantose Nigricans esteve associada à cor não-branca (p=0,003), adolescentes (p=0,003) e RI (p=0,001). Os não-brancos apresentaram chance de 5,4 vezes maior de terem Acantose Nigricans, os adolescentes, de 2,47 e os com Resistência Insulínica, de 2,66.
CONCLUSÃO: Os resultados na população em estudo indicam a necessidade de treinamento voltado à identificação da Acantose Nigricans para profissionais de saúde, pois este sinal esteve associado à Resistência Insulínica. Identificar a Acantose Nigricans desde a infância permite prevenir e tratar precocemente distúrbios cardiometabólicos, através de acompanhamento criterioso e tratamento adequado.
Palavras-chave: Acantose Nigricans; Adolescente; Criança; Resistência à insulina

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INTRODUCTION

In Brazil, overweight and obesity are considered the most important nutritional problems of childhood and have increased significantly in recent decades. [1] Excess weight is a metabolic disorder that has developed into a worrying epidemic, particularly in childhood and adolescence, since overweight at these ages is associated with the development of cardiovascular and metabolic diseases in adulthood. [2,3]

A study conducted in a diabetes prevention program showed that lifestyle interventions prevent or delay the onset of type 2 diabetes by up to 58% in Europeans. These results reinforce the importance of identifying individuals at high risk of developing diabetes at an early stage in order to implement lifestyle interventions to prevent the onset of this disease. [4] Traditionally, high-risk patients are identified through their family history of overweight or obesity. [5]

However, another indication for the early identification of diabetes mellitus (DM) is the presence of acanthosis nigricans (AN), which is characterized by dark brown, velvety and papillomatous dermatosis with hyperkeratotic plaques. [4,6,7] The common association of AN with obesity and insulin resistance (IR) may lead to the diagnosis of interconnected conditions including type 2 diabetes, metabolic syndrome (MS) and polycystic ovary syndrome. [8]

Clinically, the area most commonly affected by AN in children is the neck (93-99%), followed by the axillary area (73%). However, this dermatosis may also affect the eyelids, lips, vulva, mucosal surfaces and the backs of hands, groin, knees and elbows. Although AN is asymptomatic, pruritus may sometimes be present. The dark color of the lesions is due to hyperkeratosis rather than an increase in melanin pigmentation as previously suggested. [4]

There is evidence that hyperinsulinemia also facilitates the indirect development of AN. This hypothesis suggests that the increased levels of circulating insulin are free to bind to IGF-1 receptors, leading to epidermal proliferation in patients with AN. [9]

Studies have shown an association between hyperinsulinemia and AN; however, these findings differ with respect to the other components of the metabolic syndrome such as obesity, hypertension, elevated triglyceride levels, low HDL and high LDL levels and glucose intolerance. The presence of the metabolic syndrome in U.S. adults generates a risk of heart disease equivalent to that found with smoking and a 3.5-fold increase in the risk of developing diabetes mellitus. However, studies in children and adolescents are sparse. [10]

Consequently, evaluating the relationship between AN, IR and the components of the metabolic syndrome is critical for the management of clinical cases. Therefore, the objective of the present study was to determine the association between AN, IR and the components of the metabolic syndrome in overweight children and adolescents.

METHODS

This cross-sectional study with a quantitative approach was conducted between April 2009 and April 2010. It is part of a larger project entitled "The prevalence of cardiometabolic risk factors among obese or overweight children and adolescents". The study was carried out at the Center for Childhood Obesity (COI), located at the "Elpidio de Almeida" Institute (ISEA), Campina Grande, Paraíba, created specifically to meet the requirements of the abovementioned research project.

The study was approved by the Internal Review Board of the State University of Paraíba under reference number 0040.0.133.000-08.

Population and Sample

This population sample was recruited by providing information on the study protocol to healthcare professionals at the city's basic healthcare units. Individuals who met the inclusion criteria were invited to participate in the study and referred to the Center for Childhood Obesity (COI) by the healthcare teams. Today, the COI is a reference center for the treatment of obese children and adolescents in Campina Grande, Paraíba. In addition to the investigators, the staff at the center is composed of a multidisciplinary team that includes endocrinologists, nutritionists, psychologists, nurses, social workers and physical therapists.

A convenience sample composed of 196 children was included. Since this sample consists of obese or overweight children and adolescents receiving care within the municipal healthcare network, the ideal sample size was calculated using the Statcalc function of the Epi Info software program to verify the representativeness of the number evaluated. For this purpose, the population of 1 to 19 years of age enrolled in the basic healthcare data system (SIAB) in 2008, corresponding to 65,980 individuals, was evaluated, [1] showing prevalence rates of 25% for overweight/obesity and 42% for the metabolic syndrome. For an error of 5%, the required sample would consist of 180 individuals; [11, 12] however, this number was increased to include all the individuals in the sample. Individuals with diabetes at the time of evaluation or those in use of drugs that affect blood pressure or lipid and/or glucose metabolism were excluded.

Procedures

Anthropometric data (weight, height and waist circumference) were collected in duplicate and the mean value of the two measurements was considered in the analysis. A platform-type digital scale (Welmy™) with a weight capacity of 150 kg and precision of 0.1 kg was used to weigh the patients. Height was measured using a Tonelli™ stadiometer with precision of 0.1 cm. The individuals wore light clothing while being measured and the procedures followed were those recommended by the World Health Organization (WHO). [13]

For the classification of nutritional status, body mass index (BMI) was calculated as recommended by the Centers for Disease Control and Prevention. BMI was classified as follows: overweight (BMI ≥ 85th percentile but < 95th percentile), obesity (BMI ≥ 95thpercentile but < 97th percentile) and severe obesity (BMI ≥ 97th percentile). [14]

Waist circumference was measured using an inelastic measuring tape (Cardiomed™) with precision of 0.1 cm, placed directly on the skin. Measurements were taken at the midpoint between the top edge of the iliac crest and the last costal margin with the patient standing with his/her arms alongside the body during the expiratory phase of respiration. Values above the 90th percentile for age and sex were considered abnormal, with cut-off points of 88 cm for girls and 102 cm for boys. [15,16]

Blood pressure was measured three times with the individual at rest in the seated position, at intervals of approximately 2 minutes, in accordance with the method established by the V Brazilian Guidelines on Hypertension. Measurements were taken with an aneroid sphygmomanometer using appropriately sized cuffs, and the mean of the last two measurements was considered the final result. In the first visit, measurements were taken on both arms. If a difference was found, the arm with the highest value was always used as a reference for follow-up measures. [17]

Blood samples were collected at the clinical laboratory of the State University of Paraiba (LAC/UEPB) following a fasting period of 10-12 hours. Total cholesterol, HDL-cholesterol, triglycerides and glucose were assessed by an automated enzymatic colorimetric method (Model BioSystems 310), using commercially available reagents as directed by the manufacturer (Labtest™). All analyses were conducted at the LAC/UEPB except for insulin, which was measured at a quality-assured outsourced laboratory using the INSULIN-CT radioimmunoassay (CIS Bio International™), with radioactivity counts being determined in an Abbott™ gamma counter (intra-assay variation coefficient of 2.6%).

To assess insulin resistance, the homeostasis model of assessment - insulin resistance (HOMA-IR) was used as described by Matthews et al.[18] and validated by several authors for epidemiological studies. HOMA-IR is the product of fasting insulin (μUI / mL) and fasting plasma glucose (mmol / L) divided by 22.5. [19] HOMA-IR ≥ 2.5 was used as the cutoff point in this study. [20,21]

The metabolic syndrome was diagnosed in accordance with the criteria recommended by the National Cholesterol Education Program / Adult Treatment Panel III adapted for this age group. These criteria take into consideration the presence of at least three of the following items: waist circumference ≥ the 90th percentile for age, sex and race/ ethnicity; triglycerides ≥ 100 mg/dL and/or HDL-c < 45 mg/dL, fasting glucose ≥ 100mg/dL, systolic and/or diastolic blood pressure above the 90th percentile for sex, height and age. [16] The cutoff levels for triglycerides, HDL-c and fasting glucose followed the recommended values provided in the I Guideline For Preventing Atherosclerosis in Childhood and Adolescence. [22]

Data were shown as proportions and means ± standard deviations (SD). Insulin resistance was compared between the groups using the chi-square test or Fisher's exact test. To evaluate the level of resistance and its relationship with the components of the metabolic syndrome, HOMA-IR was distributed into quartiles, as follows: below the 25th percentile, ≥ the 25th percentile but below the 50th percentile, ≥ the 50th percentile but below the 75th percentile and ≥ the 75th percentile. HOMA-IR was then compared with the mean value of each component of the metabolic syndrome according to the quartiles using analysis of variance (ANOVA) and the Tukey post hoc test.

Statistical Analysis

Data were shown as proportions and means ± standard deviations (SD). The presence of acanthosis nigricans was compared between the groups using the chi-square test or Fisher's exact test. One-way ANOVA was used to evaluate the mean value of the components of the metabolic syndrome in relation to the presence or absence of acanthosis nigricans. Analyses were performed using the SPSS statistical software package, version 17.0 (SPSS Inc, Chicago, USA) and a significance level of 5% was adopted.

RESULTS

Of the 202 individuals who were screened for inclusion in this study, 8 were excluded, 6 due to associated diseases or the use of certain medication and 2 due to the absence of information on acanthosis nigricans in the patient's medical chart. Therefore, 194 individuals participated in this study.

Table 1 shows the sociodemographic characte-

ristics of the study sample, as well as their distribution according to age groups and the presence or absence of AN and IR.

Of the 194 children and adolescents, more than half were female (66%), non-white (63.4%) and severely obese (66.5%). Acanthosis nigricans and insulin resistance were present, respectively, in 58.2% and 42.7% of the study population (Table 1).

The presence of AN was associated with being non-white (p = 0.003, PR = 5.4), with being between 10 and 19 years of age (p = 0.003, PR = 2.47) and with the presence of IR (p = 0.001; PR = 2.66) (Table 2).

Analysis showed an association between the presence of AN and BMI (p = 0.000), insulin (p = 0.000), waist circumference (p = 0.000) and HOMA-IR (p = 0.000), the mean values of all these variables being significantly higher in patients with AN (Table 3).

DISCUSSION

It is important to identify patients at a high risk of developing diabetes as early as possible, since adopting a healthy lifestyle in childhood will prevent this disease from occurring. [4] Studies have indicated that the presence of AN is associated with obesity, IR, type 2 diabetes and the metabolic syndrome; however, further studies should be conducted to determine whether the presence of this dermatosis is a sensitive indicator of the patient's metabolic status. [4,6,7,8]

In the present study, most participants were female, brown-skinned, adolescent and severely obese. This is worrisome, since obesity in this age group tends to persist into adulthood and is associated with cardiovascular and metabolic diseases. This association is even stronger if the individual is severely obese. [3]

An association was observed in the participants of this study between AN, overweight and metabolic disorders, since 58.2% of participants had AN and 42.7% had IR. These results are similar to those reported by Zambon et al. who found that 58% of a sample of overweight children and adolescents had AN. [23] This percentage was even higher in another study conducted with individuals of 4 to 18 years of age in Belo Horizonte, Brazil, where 89.6% of participants were identified as having AN. That study differs from others by rating AN as mild, moderate or severe. Nevertheless, the variables analyzed and the inclusion and exclusion criteria were the same; therefore, the differences fail to explain the high percentage of clinical AN found. [24]

Obesity alone is not believed to be responsible for the presence of AN; however, hyperinsulinemia leads to the development of AN because the increased insulin levels activate IGF-1 receptors that are responsible for the proliferation of the epidermis, thus justifying the high prevalence of AN in individuals with insulin resistance. [9]

Studies have shown the association of acanthosis nigricans on the neck with skin color, the presence of insulin resistance and age group. These previous findings are similar to the results found in the present study in which the presence of AN was associated with being non-white (p = 0.003) and adolescent (0.003) and with the presence of IR (p = 0.001). [4,25] In comparison, a study conducted in the United States found that AN was more prevalent in non-Hispanic white individuals (p = 0.001); however, ethnic differences between North and South America do not allow reliable comparisons of race/ethnicity. Nonetheless, that study evaluated individuals of 7 to 65 years of age and revealed a remarkable frequency of AN among children and adolescents, showing that AN is an indicator of metabolic disorders that should be investigated from childhood onwards. The results showed that in adolescence, the clinical identification of AN is as common as it is in adults and is related to high insulin levels. [4]

The present findings indicate that non-white individuals are 5.4 times more likely to have AN than

Table 1: Distribution of participants according to sociodemographic characteristics, age group and the presence of acanthosis nigricans and insulin resistance (n = 194)

Characteristic	n	%
Sex		
Male	66	34
Female	128	66
Race/Ethnicity		
White	71	36.1
Brown-skinned	122	63.4
Indigenous	1	0.5
Age Group		
Preschoolers	18	9.3
School-aged	57	29.4
Adolescent	119	61.3
Nutritional status		
Overweight (BMI ≥ 85 < 95)	30	15.5
Obesity (BMI ≥ 95 < 97)	35	18.0
Severe obesity (BMI ≥ 97)	129	66.5
Acanthosis nigricans		
Present	113	58.2
Absent	81	41.8
Insulin Resistance		
Present	82	42.7
Absent	110	57.3

Table 2: Frequency and prevalence ratio of acanthosis nigricans and insulin resistance in overweight children and adolescents. COI, Campina Grande, PB, 2009-2010

Variables	ACANTHOSIS NIGRICANS (%) Present	Absent	p-value	PR 95%CI
Sex				
Male	57.6	42.4	0.890	
Female	58.6	41.4		
Race/ ethnicity				
White	32.9	67.1	0.000	5.4
Non-white	72.6	27.4		(2.86-10.21)
Age Group (years)				
10-19	66.4	33.6	0.003	2.47
2-9	44.4	55.6		(1.36-4.49)
Nutritional status				
Severe obesity (BMI ≥ 97)	62.0	38.0	0.134	
Obesity (95 ≥ BMI < 97)	50.8	49.2		
Insulin Resistance				
Present	72.0	28.0	0.001	2.66
Absent	49.1	50.9		(1.44-4.89)
Metabolic Syndrome				
Present	63.7	36.3	0.058	
Absent	49.3	50.7		
TG (mg/dl)				
Altered	61.4	38.6	0.500	
Normal	56.5	43.5		
SBP (mmHg)				
Altered	55.4	44.6	0.528	
Normal	60.0	40.0		
DBP (mmHg)				
Altered	56.8	43.2	0.582	
Normal	60.9	39.1		
HDL (mg/dl)				
Altered	59.6	40.4	0.434	
Normal	52.6	47.4		
Glucose (mg/dl)				
Altered	33.3	67.7	0.378	
Normal	58.6	41.4		

Legend: COI = Centre for Childhood Obesity, p-value = significance, PR = prevalence ratio, CI = confidence interval, BMI = body mass index, TG = triglycerides, DBP = diastolic blood pressure, SBP = systolic blood pressure, HDL = high-density lipoprotein.

white individuals, and this result is similar to findings from a study conducted with obese Brazilian females, in which black participants were found to be 5-times more likely to have AN compared to white participants. This fact is explained by genetic characteristics, since black individuals are more likely to form hyperkeratotic plaques. [25]

With regard to age, adolescents were 2.47 times more likely to present with this dermatosis. The study conducted in Belo Horizonte with obese children and adolescents reported similar findings. Hyperinsulinemia was found to be more severe in older indi-

Table 3: Mean blood pressure, laboratory and anthropometric data according to the presence or absence of acanthosis nigricans in overweight children and adolescents. COI, Campina Grande, PB, 2009-2010

	ACANTHOSIS NIGRICANS (%)		
Variables	**Present Mean (± SD) (95%CI)**	**Absent Mean (± SD) (95%CI)**	**p-value**
BMI	28.5 (±4.7) (27.6-29.3)	25.5 (±4.0) (24.6-26.3)	0.000
DBP (mmHg)	72.8 (±10.0) (70.9-74.7)	71.8 (±9.6) (69.6-73.9)	0.480
SBP (mmHg)	109 (±11.6) (106.9-111.1)	106.7 (±12.4) (104.0-109.5)	0.197
TG (mg/dl)	130.8 (±69.75) (107.8-143.8)	121.3 (±61.9) (107.7-135.1)	0.330
HDL (mg/dl)	37.8 (±10.15) (35.9-39.7)	39.42 (±6.7) (37.9-40.9)	0.230
Glucose (mg/dl)	81.5 (±7.2) (80.1-82.7)	80.4 (±7.8) (78.6-82.2)	0.333
WC (cm)	88.69 (±12.7) (86.3-91.1)	81.2 (±12.8) (78.2-83.9)	0.000

Legend: COI = Center for Childhood Obesity, SD = standard deviation, BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure, TG = triglycerides, HDL = high-density lipoprotein; WC = waist circumference.

viduals, thus explaining the increased risk of AN in adolescents compared to younger children. [24]

It is important to emphasize that participants with IR had a 2.66-fold greater risk of having AN and that this finding corroborates the results of Viana et al., who found AN to be associated with high fasting insulin levels and post-load values. [24] In the same study, children and adolescents with higher mean HOMA-IR scores were 1.4 times more likely to have AN. Another study carried out in the United States with individuals of 7 to 65 years of age showed that the presence of AN was associated with higher insulin levels. [4]

With regard to the mean values of the clinical variables, the presence of AN was found to be associated with higher mean BMI (p = 0.000) and waist circumference (p = 0.000). According to Higgins et al., AN becomes more prevalent as mean BMI and waist circumference increase, since overweight individuals are more susceptible to IR. [8]

In addition, the mean values of the other components of the metabolic syndrome were not associated with the presence of AN, and this finding is similar to the results encountered in a study conducted in the United States with 3,601 adults in which no association was found with the following components of the metabolic syndrome: hypertension, high triglyceride levels, low HDL levels, high LDL levels and glucose intolerance. Only hyperinsulinism was found to be positively associated with the presence of AN. [10]

According to the results presented here, the presence of AN may contribute towards facilitating the early detection of conditions that increase the risk of overweight children and adolescents of developing cardiometabolic diseases in adulthood, thus permitting the timely implementation of interventions. [8]

The evaluation of overweight children and adolescents was considered a limitation of the present study, since it did not permit these variables to be evaluated in individuals of normal weight. Nevertheless, this study calls attention to the importance of identifying AN in childhood in order to prevent cardiometabolic disorders in adulthood. This study has the usual limitations of all cross-sectional studies, identifying and discussing associations between events and suggesting hypotheses that then need to be further investigated in longitudinal studies.

CONCLUSION

The presence of acanthosis nigricans (AN) in the population was associated with higher BMI and waist circumference and proved to be a good indicator for the identification of children and adolescents with IR, thus permitting those at a greater risk of developing type 2 diabetes to be identified at an early stage. Although this condition is not associated with other components of the metabolic syndrome, mean triglyceride and fasting glucose levels and systolic and diastolic blood pressure were higher among individuals with AN, while HDL levels were lower.

According to these results, acanthosis nigricans should be used as a predictor of metabolic disorders in overweight children and adolescents. Therefore, health professionals should be trained to identify AN, since this condition is associated with overweight children and adolescents and with an adverse metabolic profile. ❑

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