# Metabolic syndrome and subclinical carotid atherosclerosis in Mexican children and adolescents with acanthosis nigricans

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## Abstract

**Introduction:** *Acanthosis nigricans is a marker of insulin resistance that is associated with metabolic and cardiovascular alterations.* **Objective:** *To investigate the frequency of metabolic syndrome and subclinical carotid atherosclerosis in children and adolescents with acanthosis nigricans, and to compare the results between genders.* **Method:** *Cross-sectional study, where 30 male and 30 female subjects younger than 18 years of age diagnosed with acanthosis nigricans were included. The presence of metabolic syndrome (Cook's criteria), cardiovascular risk (ultrasensitive C-reactive protein and [us-CRP]), and carotid atherosclerosis (intima-media thickness [IMT]) was investigated. Descriptive and inferential statistics was used for data analysis.* **Results:** *The frequency of metabolic syndrome was 43% (males 42 % versus females 58%, p = 0.58). All patients showed us-CRP abnormal levels: 67% were classified with moderate cardiovascular risk and 27% with high risk. The prevalence of carotid atherosclerosis was 98% (males 49% versus females 51%, p = 0.45). Acanthosis nigricans severity did not influence on the results.* **Conclusions:** *Intentional search for metabolic syndrome and subclinical carotid atherosclerosis in Mexican children and adolescents with acanthosis nigricans, regardless of gender or disease severity, will enable the implementation of measures to decrease the morbidity and mortality seen in adult age.*

***KEY WORDS:*** *Acanthosis nigricans. Metabolic syndrome. Carotid atherosclerosis. Children. Adolescents.*

## Introduction

Acanthosis nigricans (AN) is considered to be a cutaneous manifestation of obesity and insulin resistance.[1] The latter is the common pathogenic pathway between AN, metabolic syndrome (MS) and atherosclerosis,[2] given that high serum insulin levels have the following effects:

- They stimulate insulin-like growth factor 1 receptors in dermal keratinocytes and fibroblasts, which favors the development of AN.[3]
- They produce inappropriate lipolysis with an increase in triglycerides and a decrease in high-density lipoprotein (HDL), which facilitate the development of MS.[4]
- They contribute to progressive development of atherogenesis and allow the release of pro-inflammatory cytokines that perpetuate insulin resistance and result in higher endothelial dysfunction.[5]

Given that AN has increased in parallel with obesity increase in the pediatric population[3] and that, according to the Organization for Economic Cooperation and Development, 29 % of girls and 28 % of boys in Mexico are estimated to experience overweight or obesity,[6] we would expect a higher presence of metabolic and cardiovascular disorders in this age group, albeit

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in a search in the literature we did not find data in that regard in Mexican pediatric population with AN. Therefore, our purpose was to investigate the frequency of MS and carotid atherosclerosis in Mexican children and adolescents with AN, and to compare the results between both genders and with those published in the literature.

## Method

Cross-sectional study at Instituto Dermatológico de Jalisco "Dr. José Barba Rubio", after authorization of the Ethics Committee of the institution and signature of consent once the parent or legal guardian of each participant was informed. A convenience sample of 60 patients diagnosed with AN (30 males and 30 females), Mexicans by birth and with two previous generations of Mexican origin, from 0 to 17 years of age, without prior treatment for AN or other dermatoses associated with obesity, diabetes or lipid disorders was included.

Subjects who in the interview referred having been diagnosed with congenital or acquired disease during the AN evolution, metabolic or lipid alterations or atherosclerosis and those who consumed medications to lose weight, or blood glucose-lowering, antihypertensive or lipid-lowering drugs, growth hormone, sex hormones or glucocorticoids, which are associated with the development of AN. were excluded. Patients with ultrasensitive C-reactive protein (usCRP) values > 10 mg/L were eliminated, due its association with acute inflammatory processes.[7]

AN diagnosis was clinical and was carried out by a trained dermatologist. Neck involvement and severity having a score ≥ 1 were considered as conditions for diagnosis. To determine the severity five anatomical sites were taken into account: the neck, axillae, elbows, knuckles and knees. The neck was assessed with regard to extension (0 to 4 scale) and severity (texture with a scale from 0 to 3). In the axilla, only the extension was assessed (0 to 4 scale). On elbows, knuckles and knees only presence (1 point) or absence (0 points) was determined. To define AN severity grades, total evaluation score was classified as absent (<1), mild (1-1.5), moderate (1.6-1.9) and severe (≥ 2).[8]

The metabolic syndrome diagnosis was established based on Cook's criteria,[9] with the presence of 3 or more of the following parameters:

- Waist circumference ≥ 90$^{th}$ percentile for age and gender. With a non-distensible material measuring tape and the patient in the stand-up position, waist circumference was measured from the midpoint between the twelfth rib and the edge of the iliac crest, going through the navel, after a normal exhalation.[10]
- Arterial hypertension ≥ 90$^{th}$ percentile for age, gender and height.[9] It was taken in a sitting position, with a mercury sphygmomanometer with appropriate cuff for the patient arm length and age, after a 10-minute period of rest. Blood pressure was classified according to normal values for age, gender and height, using the methodology standardized by the Second Task Force.[11]
- Triglycerides ≥ 110 mg/dL.[9] They were determined using an enzymatic colorimetric method. For their measurement, a peripheral venous blood sample of 10 mL was obtained after a 12-hour fasting, which also served for the performance of the rest of laboratory tests.
- HDL cholesterol ≤ 40 mg/dL[9] and glucose ≥ 110 mg/dL.[9] Both were determined by enzymatic colorimetric method.

Atherosclerosis was determined with the carotid intima-media thickness (IMT), defined as the size of the distal wall of the left and right common carotid artery.[12] It was measured with the patient at rest in the decubitus position, with a longitudinal scan of the right and left common carotid artery being performed with B-mode ultrasound (Philips iE33 Apparatus with L11-3Transducer, ® Yorba Linda, CA) along one centimeter. Measurements were made at three points and average value was calculated to obtain the IMT measurement.[13-15] Carotid IMT > 0.37 mm was considered abnormal in boys and girls up to 6 years of age, > 0.41 mm in boys from 6 to 17 years 11 months of age and > 0.39 mm in girls from 6 to 17 years 11 months of age.[16]

Cardiovascular risk was indirectly determined with usCRP serum levels.[17-19] A 10 mL sample of peripheral venous blood obtained after a 12-h fasting was processed by nephelometry. Individuals were defined to have low cardiovascular risk if their levels were < 1 mg/L, with moderate risk if levels were 1-3 mg/L and with high risk if levels were > 3 mg/L. Patients with levels > 10 mg/L were excluded, since such levels are associated with acute inflammatory processes.[7]

To compare the proportions, the chi-square test or Fisher's exact test were employed. Student's t-test was used to compare continuous variables with normal distribution. As a measure of association, the odds ratio (OR) with 95 % confidence interval (CI) was obtained. A p-value < 0.05 was considered to be a statistically significant difference.

**Table 1. Study variables distribution by acanthosis nigricans severity**

| Component | Mild AN (n = 16) | | Moderate AN (n = 13) | | Severe AN (n = 31) | | p* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Metabolic syndrome (n = 26) | 7 | 27 | 7 | 27 | 12 | 46 | 0.73** |
| Moderate cardiovascular risk (n = 40) | 11 | 27.5 | 9 | 22.5 | 20 | 50 | 0.77** |
| High cardiovascular risk (n = 16) | 4 | 25 | 3 | 19 | 9 | 56 | 0.52*** |
| Carotid atherosclerosis (n = 59) | 16 | 27 | 13 | 22 | 30 | 51 | 0.65*** |

*The p-value is the result of the comparison between mild versus severe AN. **Chi-square test. ***Fisher's exact test.
AN = Acanthosis nigricans.

**Table 2. Study variables by gender in children and adolescents with metabolic syndrome**

| Component | Males (n = 11) | | Females (n = 15) | | p* |
|---|---|---|---|---|---|
| | Mean ± SD | Min-Max | Mean ± SD | Min-Max | |
| Waist circumference (cm) | 102 ± 12 | 85-124 | 96 ± 14 | 64-128 | 0.28 |
| Systolic BP (mmHg) | 117 ± 15 | 92-148 | 103 ± 16 | 70-132 | 0.03 |
| Diastolic BP (mmHg) | 69 ± 10 | 58-88 | 60 ± 10 | 40-78 | 0.04 |
| Triglycerides (mg/dL) | 171 ± 42 | 114-256 | 152 ± 53 | 65-267 | 0.34 |
| HDL cholesterol (mg/dL) | 34 ± 5 | 25-40 | 32 ± 5 | 19-39 | 0.36 |
| Glucose (mg/dL) | 88 ± 5 | 79-94 | 89 ± 8 | 76-111 | 0.73 |
| Right carotid IMT (mm) | 0.44 ± 0.03 | 0.40-0.51 | 0.43 ± 0.02 | 0.40-0.48 | 0.76 |
| Left carotid IMT (mm) | 0.43 ± 0.03 | 0.40-0.52 | 0.44 ± 0.03 | 0.40-0.53 | 0.53 |
| usCRP (mg/L) | 4.03 ± 2.86 | 1.5-9.5 | 2.85 ± 1.59 | 1-7.2 | 0.31 |

*Two-tailed Student's t-test.
BP = Blood pressure, HOMA = Homeostasis Model Assessment, IMT = Intima-media thickness, usCRP = Ultrasensitive C-reactive protein.

## Results

Age average was 11.5 ± 3 years (range: 4 to 17). AN was mild in 16 subjects (26.6 %), moderate in 13 (21.6 %) and severe in 31 (51.6 %). MS was diagnosed in 26 subjects (43 %), with no difference between genders: 11 males (42 %) versus 15 females (58 %, p = 0.58). The frequency of MS components was: low HDL in 26 subjects (100 %), obesity in 25 (96 %), elevated triglycerides in 24 (92 %), arterial hypertension in 10 (38 %) and hyperglycemia in one (4%).

usCRP had average levels of 3.07 ± 2.03 mg/L (range: 1 to 9.5). All subjects had altered usCRP: 40 (67 %) had moderate cardiovascular risk levels and 16 (27 %) had high cardiovascular risk levels; 4 subjects (6%) were eliminated for having usCRP levels > 10 mg/L. Of the 56 subjects with altered usCRP, there were equal numbers by gender: 28 (50 %, p = 1.0).

Right common carotid average IMT was 0.44 ± 0.04 mm (range: 0.40 to 0.65 mm), whereas left common carotid average IMT was 0.44 ± 0.03 mm (range: 0.40 to 0.55 mm). Abnormal carotid IMT values for age and gender were found in 59 patients (98 %). Out of them, 29 (49 %) were males and 30 (51 %) females (p = 0.45).

AN severity did not influence on the investigated variables (Table 1). Among the children with MS, average blood pressure figures were statistically higher in the male gender (Table 2). Elevated triglyceride and decreased HDL levels were the alterations that conferred children with AN higher possibility for developing MS (Table 3).

## Discussion

The frequency of MS in Mexican children and adolescents in our study was 43 %, which is lower than that reported in Brazilian children with AN (67.3 %),[20] but both are superior to those found in open pediatric population. For example, in Mexican-American population, MS was reported in 18.7 %,[21] whereas in Mexican population, in 19.6%,[22] which are foreseeable results if we consider that in the pathogenesis of MS obesity and insulin resistance are mainly involved,[23] and both these factors are present in children with AN.

**Table 3. Distribution of variables in the presence of metabolic syndrome**

| Component | With MS (n = 26) | | | Without MS (n = 34) | | | p | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | % | n | % | % | | | |
| Male gender | 11 | | 42 | 19 | | 56 | 0.58 | __ | |
| Female gender | 15 | | 58 | 15 | | 44 | 0.58 | __ | |
| Mild AN | 7 | | 27 | 9 | | 26 | 0.79 | __ | |
| Moderate AN | 7 | | 27 | 6 | | 18 | 0.36 | __ | |
| Severe AN | 12 | | 46 | 19 | | 56 | 0.58 | __ | |
| Waist circumference ≥ 90 | 25 | | 96 | 25 | | 74 | 0.03* | 9 | 1-205 |
| Arterial hypertension ≥ 90 | 10 | | 38 | 2 | | 6 | 0.001** | 19 | 2-429 |
| Triglycerides ≥ 110 mg/dL | 24 | | 92 | 14 | | 41 | 0.00004** | 30 | 3-660 |
| HDL cholesterol ≤ 40 mg/dL | 26 | | 100 | 14 | | 41 | 0.00003** | > 30*** | |
| Glucose ≥ 110 mg/dL | 1 | | 4 | 0 | | 0 | 0.42 | __ | |
| Insulin resistance | 18 | | 69 | 15 | | 44 | 0.05** | 3 | 0.86-10 |
| Carotid atherosclerosis | 25 | | 96 | 34 | | 100 | 0.04** | 3 | 0.89-11 |
| Moderate cardiovascular risk | 14 | | 54 | 26 | | 76 | 0.10 | __ | |
| High cardiovascular risk | 8 | | 31 | 8 | | 24 | 0.49 | __ | |

*Two-tailed Fisher's exact test, **Chi-square test, ***Inexact. MS = Metabolic syndrome, AN = acanthosis nigricans, HDL = high-density lipoprotein.

The importance of this MS frequency is that individuals who suffer from it in childhood have a 2.7 to 3.4 higher risk of experiencing it at adulthood, as well as twice the risk for developing carotid atherosclerosis and two to three times more risk for developing diabetes,[24] in addition to a significantly higher risk of cardiovascular events, with a prevalence of 19.4 %, whereas in those without MS it is 1.5 %.[25]

The most common MS components were low levels of HDL, obesity and high levels of triglycerides, with no significant difference between genders. The systolic blood pressure and diastolic blood pressure figures were statistically higher in the male gender. This last finding is similar to that reported by Halley et al.,[22] who observed a frequency of arterial hypertension significantly higher in male Mexicans, but not in the rest of its components.

Obesity, elevated levels of triglycerides and decreased levels of HDL are factors that increase the risk for MS in adulthood. In agreement with the Bogalusa Heart Study, obesity confers an 11-fold higher risk for the appearance of this syndrome in adulthood.[26] According to the Finnish Study on Cardiovascular Risk in Young People, elevated triglycerides, low HDL cholesterol and high blood pressure figures are MS predictors.[27] In our study, these components conferred higher possibility in children and adolescents with AN for the development of MS, in some cases up to 30-fold higher risk.

As for usCRP, accumulated evidence suggests that its measurement represents a cardiovascular risk predictor that is even more powerful than LDL values, both in patients with coronary disease and in apparently healthy subjects.[28] In our study all children and adolescents with AN showed usCRP levels considered of moderate or high risk. We did not observe any difference in usCRP levels between children with and without MS, but in a study that included Spanish children, the authors observed that those with obesity and MS had higher usCRP figures than those with obesity without MS, and thus the test is considered useful for cardiovascular risk factors early detection in this age group.[29]

Regarding atherosclerosis, the process starts since childhood, long before clinically identifiable signs and symptoms occur. In autopsies carried out in young subjects, atherosclerosis at early stages was shown to be related to obesity, triglycerides elevated levels and decreased HDL cholesterol levels.[30] These metabolic alterations were present in the children and adolescents included in our study, which might explain that the fact that 98 % had subclinical carotid atherosclerosis. We did not find analyses evaluating carotid IMT in children with AN, but its determination is important because it is a predictor of cardiovascular and

stroke risk, and due to its positive correlation with both classic and emerging risk factors.[23,30-32]

These alterations in Mexican children and adolescents with AN have an impact on economy, since in Mexico premature death associated with overweight and obesity in 2008 involved a loss of productivity of US$ 1931 million.[33] Therefore, implementation of effective actions for prevention during childhood should be a priority of health systems, since prevention programs might avoid between 47 000 and 55 000 deaths from chronic diseases per year.[34]

Although longitudinal studies with larger number of patients are required to corroborate the results, systematic exploration of children and adolescents looking for AN might help timely detection of metabolic and cardiovascular alterations, which would enable the implementation of measures to prevent morbidity and mortality in adulthood.

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