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Acanthosis nigricans in the knuckles: An early, accessible, straightforward, and sensitive clinical tool to predict insulin resistance

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ABSTRACT

Any clinical/biochemical marker revealing obesity or diabetes before their appearance is valuable. Insulin resistance (IR) is present in both disorders many years before occurrence. Accordingly, we determined whether acanthosis nigricans (AN) in the knuckles is associated to higher insulin and homeostasis model assessment for estimated insulin resistance (HOMA-IR) index values, and assessed the influence of body-mass index (BMI) and the diagnostic performance of AN in the knuckles to detect IR. In this cross-sectional controlled study, we included men or women, 18 to 23 years old, with or without AN in the knuckles. In 149 cases with AN in the knuckles and 145 controls, fasting insulin was higher in cases (13.45 μU/mL $\pm$ 7.8 *vs.* 8.59 μU/mL $\pm$ 3.63, $P < .001$, respectively). Mean HOMA-IR index was also higher (2.86 $\pm$ 1.68 *vs.* 1.78 $\pm$ 0.77, $P < .001$). A significant increase in fasting insulin and HOMA-IR values between and within BMI groups from normal through obese category was identified in controls and cases. By multivariate regression analysis, cases with normal BMI were significantly associated to a HOMA-IR $\geq$2.5 (OR = 3.09, CI95% = 1.75–5.48, $P = .001$). A model of AN in the knuckles, normal BMI, and increased waist circumference allowed identifying 2 out of 3 cases with HOMA-IR index $\geq$2.5. AN in the knuckles could be addressed with two aims: as an easy, accessible, and costless diagnostic tool suggesting hyperinsulinemia secondary to IR, and, an early marker of IR even in the absence of overweight or obesity.

1. Introduction

Public health systems worldwide face an increase in obesity and diabetes as well as their late clinical metabolic and mechanical consequences.[1,2] Early detection, before clinical expression of progressive weight gain, is the most reliable way to prevent morbidity, mortality and its implications.[1,2] Therefore, any marker or high-risk signal that reveals these diseases before overt clinical appearance would be foremost valuable. One of these initial abnormalities could be insulin resistance (IR), a primary feature linked to early stages of obesity, type 2 diabetes, hypertension, dyslipidemia, cancer, and other illnesses.[3-7]

Polycystic ovary syndrome, androgenetic alopecia, non-alcoholic steatohepatitis, and acanthosis nigricans (AN) have been associated to IR in early stages of the pathophysiology that can later lead to its cardiovascular and metabolic complications.[7-10] AN is a well-accepted expression of compensatory hyperinsulinemia due to IR.[11] Although publications classically describe the neck, axilla, elbow, and groin as the most frequent sites, this is not based on studies assessing their prevalence and clinical value.[12-16] A recent study of our group demonstrated that, in a large series of young Latino participants, AN in the knuckles is a usually ignored, easy to examine finding, with the highest prevalence, particularly in overweight and normal body mass index (BMI) subjects, when contrasted to the other classical sites.[17] Unfortunately, IR biochemical markers were not determined. A

comparison of these indicators, particularly in normal and overweight subjects, would be crucial to provide support that AN in the knuckles represents early expression of compensatory hyperinsulinemia in response to IR. Furthermore, there are no studies comparing IR indexes among individuals with and without AN in the knuckles focusing on different BMI categories.

This cross-sectional controlled study contrasts, as a primary endpoint, fasting insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR) index, a well-recognized method to estimate insulin resistance, in Latin American medical students with and without AN in the knuckles. Secondary endpoints were to assess fasting insulin levels and HOMA-IR index between BMI categories in participants with or without AN in the knuckles; compare fasting insulin levels and the HOMA-IR index in controls *vs.* cases with variable AN presentations: in the knuckles alone and when also present in other classical sites; and evaluate the clinical value of AN in the knuckles for IR prediction.

2. Results

2.1. Allocation analysis

Three hundred nineteen subjects were enrolled in the study, 149 cases (50.7%) and 145 controls (49.3%). Among the cases, 68 (45.6%) had AN in the knuckles alone (AN1) and 81 (54.4%) had AN in the knuckles and in other classical sites (AN2). Twenty-five subjects did not have AN in the knuckles but present in any other classical site (AN3). Hence, the total studied population was 294. Regarding classification of case or control, concordance between the three observers was 90% (kappa = 0.79), 87% (kappa = 0.75) and 86.5% (kappa = 0.75).

2.2. Study population

The characteristics of the population overall and according to AN allocation are shown in Table 1. Mean age was 20.2 ± 1.4 years and 54% were men. Almost 80% were between 18 and 21 years of age with level 3 and 4 skin phototype. Overweight or obesity occurred in 40.1% (26.5% and 13.6%, respectively). Normal BMI occurred in 47.7% and 72.4% of cases and controls, respectively ($P < .001$). Increased waist circumference (IWC) was present in 49.7% and 24.8% of cases and controls, respectively ($P < .001$).

Table 1. Epidemiological characteristics of the study population as a whole and by groups.

	All patients (n = 294)	Controls (n = 145)	Cases (n = 149)	P value
Sex, No. (%)				
Female	134 (45.6)	67 (46.2)	67 (45)	0.9
Age, mean (SD), y	20.2 (1.4)	20.2 (1.4)	20.3 (1.4)	0.48
BMI[a], mean (SD)	24.7 (4.7)	23.4 (3.7)	26.1 (5.2)	<0.001
BMI[a], No. (%)				
Normal	176 (59.9)	105 (72.4)	71 (47.7)	<0.001
Overweight	78 (26.5)	28 (19.3)	50 (33.6)	
Obese	40 (13.6)	12 (8.3)	28 (18.8)	
WC, mean (SD), cm	81.7 (13.3)	77.4 (11.6)	85.9 (13.6)	<0.001
IWC, No. (%)	110 (37.4)	36 (24.8)	74 (49.7)	<0.001
BP, mean (SD), mmHg				
Systolic	115.4 (12.7)	113.9 (12.4)	116.8 (13.0)	0.046
Diastolic	70.7 (9.9)	68.3 (7.5)	73.0 (11.4)	<0.001
Photoype, No. (%)				
2	52 (17.7)	30 (20.7)	22 (14.8)	0.007
3	174 (59.2)	94 (64.8)	80 (53.7)	
4	61 (20.7)	19 (13.1)	42 (28.2)	
5	7 (2.4)	2 (1.4)	5 (3.4)	
AN1, No. (%)			68 (45.6)	
AN2, No. (%)			81 (54.4)	

Abbreviations: BMI, Body-mass index; WC, Waist Circumference; IWC, Increased Waist Circumference; BP, Blood Pressure; AN1, Acanthosis Nigricans Group 1; AN2, Acanthosis Nigricans Group 2.
[a]Calculated as weight in kilograms divided by height in meters squared.

2.3. Fasting insulin and HOMA-IR index

The mean fasting insulin and HOMA-IR index in cases, including AN1 and AN2 subgroups, and controls are shown in Table 2. The mean fasting insulin level was significantly higher in cases than controls (13.45 μU/mL ± 7.8 *vs.* 8.59 μU/mL ± 3.63, respectively, $P < .001$). The mean HOMA-IR index was also higher in cases (2.86 ± 1.68 *vs.* 1.78 ± 0.77, respectively, $P < .001$). In multivariate regression, where BMI and insulin or HOMA-IR were assessed, we identified no dependence between BMI and higher levels of insulin or HOMA-IR among cases: overweight BMI (OR 1.72, CI95%: 0.86–3.43, $P = .124$), obese BMI (OR 2.17, CI95%: 0.81–5.8, $P = .123$). A HOMA-IR index ≥2.5 was found in 52.3% of cases and 20.7% of controls ($P < .001$). Among cases, the mean fasting insulin values were significantly lower in AN1 than AN2 (10.11 μU/mL ± 4.49 *vs.* 16.25 μU/mL ± 8.85, $P < .001$), respectively, but in AN1 were greater than controls (8.59 μU/mL ± 3.64; $P = .009$). The HOMA-IR index was also lower in AN1 *vs.* AN2 (2.15 ± 1.0 *vs.* 3.45 ± 1.91, $P < .001$), but AN1 was greater than controls (1.78 ± 0.77; $P = .004$). A HOMA-IR index ≥2.5 was found in 29.4% of AN1 cases, and 71.6% of AN2 cases ($P < .001$).

Table 2. Mean fasting insulin and HOMA-IR values in the study population.

n =	Controls 145	Cases 149	AN1 68	AN2 81
Insulin, mean (SD), μU/ml	8.6 (3.6)	13.5 (7.8)[a]	10.1 (4.5)	16.3 (8.9)[b]
HOMA-IR[c], mean (SD)	1.8 (0.8)	2.9 (1.7)[a]	2.2 (1.0)	3.5 (1.9)[b]
$\geq$2.5, No. (%)	30 (20.7)	78 (52.3)[a]	20 (29.4)	58 (71.6)[b]
1.5–2.49, No. (%)	58 (40)	46 (30.9)	31 (45.6)	15 (18.5)[d]
<1.5, No. (%)	57 (39.3)	25 (16.8)[e]	17 (25)	8 (9.9)[d]

Abbreviations: AN1, Acanthosis Nigricans Subgroup 1; AN2, Acanthosis Nigricans Subgroup 2; HOMA-IR, Homeostasis model assessment of insulin resistance.
SI conversion factors: To convert insulin to pmol/L, multiply value by 6.945.
[a]Comparison between cases and controls with $P < .001$.
[b]Comparison between controls, AN1 and AN2 cases with $P \leq .001$.
[c]HOMA-IR formula: Fasting insulin (mIU/L) x fasting glucose (mg/dL) / 405.
[d]Comparison between controls, AN1 and AN2 cases with $P < .05$.
[e]Comparison between cases and controls with $P < .05$.

2.4. AN3 group vs. cases group

Age, gender, BMI, and waist circumference in AN3 group were not significantly different when compared to cases. Neither mean fasting insulin values in AN3 group (12.20 ± 4.6) nor HOMA-IR index (2.55 ± 0.98) were significantly different when contrasted to cases ($P = .43$ and 0.37), respectively. AN3 mean fasting insulin value and HOMA-IR index were not significantly higher than AN1 cases value (10.1 ± 4.5, $P = .69$ and 2.2 ± 1.0, $P = .99$, respectively) but significantly lower than AN2 cases (16.3 ± 8.9, $P = .011$ and 3.5 ± 1.9, $P = .008$, respectively).

2.5. Fasting insulin/HOMA-IR index by BMI

Table 3 shows the comparison of mean fasting insulin values and HOMA-IR indexes in different BMI categories of cases and controls. When the total population was analyzed according to their BMI, AN was found in 40.3% (71 out of 176) with normal BMI, in 64.1% (50 out of 78) overweight, and in 70% (28 out of 40) with obesity. AN1 was found in 26.1% (46), 23.1% (18), and 10% (4) of the normal, overweight, and obese BMI groups, respectively. AN2 occurred in 14.2% (25), 41% (32), and 60% (24) of the normal, overweight, and obese BMI categories, respectively. A significant progressive increase in mean fasting insulin levels and HOMA-IR between BMI groups from normal through obese was identified in controls, cases and the AN2 subgroup but not in AN1. Comparisons of serum insulin levels and HOMA-IR between cases and controls within each BMI group was also significant and between controls, AN1 and AN2. The proportions of HOMA-IR values above or below 2.5

Table 3. Mean fasting insulin and HOMA-IR values in controls, cases, AN1 and AN2 subgroups.

	Normal BMI			
n =	Controls 105	Cases 71	AN1 46	AN2 25
Insulin, mean (SD), μU/ml	8.0 (3.5)	10.7 (5.5)[a]	9.4 (3.7)	13.0 (7.3)[b]
HOMA-IR[c], mean (SD)	1.66 (0.8)	2.3 (1.2)[a]	2.0 (0.9)	2.8 (1.5)[b]
	Overweight BMI			
n =	28	50	18	32
Insulin, mean (SD), μU/ml	9.5 (3.2)	13.9 (6.0)[a]	11.3 (5.9)	15.3 (5.7)[b]
HOMA-IR[c], mean (SD)	2.0 (0.67)	2.9 (1.3)[a]	2.3 (1.2)	3.2 (1.3)[b]
	Obese BMI			
n =	12	28	4	24
Insulin, mean (SD), μU/ml	11.9 (3.9)	19.7 (11.3)[d]	12.9 (4.3)	20.9 (11.8)[e]
HOMA-IR[c], mean (SD)	2.4 (0.7)	4.3 (2.4)[a]	3.0 (0.7)	4.5 (2.6)[e]
	Analysis between BMI categories			
Insulin, mean (SD), μU/ml	0.001	<0.001	0.1	0.005
HOMA-IR[c], mean (SD)	0.002	<0.001	0.1	0.005

Abbreviations: AN1, Acanthosis Nigricans Subgroup 1; AN2, Acanthosis Nigricans Subgroup 2; HOMA-IR, Homeostasis model assessment of insulin resistance.
SI conversion factors: To convert insulin to pmol/L, multiply value by 6.945.
[a]$P \leq .001$
[b]Comparison of controls, AN1 and AN2 with $P \leq .001$.
[c]HOMA-IR formula: Fasting insulin (mIU/L) x fasting glucose (mg/dL) / 405.
[d]$P \leq .05$.
[e]Comparison of controls, AN1 and AN2 with $P < .05$.

between controls and cases by BMI groups are shown in Table 4. The proportion of participants with a HOMA-IR value above 2.5 was significantly higher in cases in the overweight ($P = .001$) and obese ($P = .008$) groups. In the normal BMI category this comparison was significant with AN2 ($P = .003$) but not with AN1 + AN2 cases ($P = .094$). There were 12 out of 25 AN2 cases (48%) and 18 out of 105 controls (17.1%) with normal BMI who had an elevated HOMA-IR index ($P = .003$).

2.6. Clinical value of AN in the knuckles in IR identification

Overweight, obesity, IWC and AN in the knuckles were designated to define the value of IR prediction. Table 5 presents the odds-ratio of the bivariate and multiple regression analysis of these clinical features. Cases with normal BMI (AN1 + AN2) were significantly associated to a HOMA-IR $\geq$ 2.5 (OR = 3.09, CI 95% = 1.75 – 5.48, $P = .001$) as well as participants with IWC (OR = 4.83, CI 95% = 2.41 – 9.7, $P < .001$). AN1, as an isolated subgroup, overweight

Table 4. HOMA-IR indexes above or below 2.5 between cases and controls by BMI groups.

BMI	n		HOMA-IR <2.5	P value ≥2.5	
Normal	176	Controls, N (%)	87 (83)	18 (17)	0.09
		Cases, N (%)	51 (72)	20 (28)	
Overweight	78	Controls, N (%)	21 (75)	7 (25)	0.001
		Cases, N (%)	16 (32)	34 (68)	
Obesity	39	Controls, N (%)	7 (58)	5 (42)	0.008
		Cases, N (%)	4 (14)	24 (86)	

Abbreviations: BMI, Body Mass Index; HOMA-IR, Homeostasis model assessment of insulin resistance

and obesity were not significantly associated; AN1 (OR = 1.37, CI 95% = 0.62 – 2.94, P = .413) in contrast to AN2 (OR = 6.09, CI 95% = 2.7 – 13.7, P < .001). In this study, the probability of having HOMA-IR ≥ 2.5 when just a normal BMI or overweight was present was 11% and 17%, respectively. A normal BMI with AN in the knuckles and IWC, however, produced a probability of 64%. In this model, when normal BMI was switched for overweight, probability increased to 76%. Taking a HOMA-IR value ≥ 2.5 as an indicator of IR, AN at least in the knuckles, had a sensitivity of 72%, a specificity of 62%, a positive predictive value of 52%, and a negative predictive value of 79%.

3. Discussion

In this large controlled study a significantly high HOMA-IR index and fasting serum insulin were observed when cases with AN in the knuckles were compared to controls. In accordance with this study, a previous study in a similar population, found that AN in the knuckles had the highest prevalence in normal BMI and overweight participants, and as frequent as the most prevalent sites (axillae/neck) in obese participants.[17] The primary endpoint, however, was to find the prevalence of AN in classical sites and in the knuckles. Insulin and HOMA-IR index were not determined. Normal BMI subjects had a prevalence of AN in the knuckles of 25%. Even more interesting, 7 out of 40 participants with a low BMI had AN in that location.[17] These findings could indicate AN in the knuckles as an ignored, early and highly prevalent clinical feature suggesting IR. To date, there are no studies looking for the clinical differential value of AN in classical and non-classical sites. AN in any place in the body is taken as an overall diagnosis; unfortunately, many times the knuckles are overseen and obviated in physical examination.[13,16,18-22] In fact, without reliable evidence, some authors mention that AN does not exist unless the neck is involved.[16,23]

Table 5. Associations and probabilities of clinical variables with insulin resistance by regression analysis.

	Bivariate analysis			Multivariate analysis[a]			
	OR	95% CI	P value	OR	95% CI	P value	β
OW	4.02	2.27–7.12	<0.001	1.72	0.86–3.43	0.1	0.54
OB	9.57	4.38–20.92	<0.001	2.17	0.81–5.8	0.1	0.77
AN[b]	4.21	2.52–7.05	<0.001	3.09	1.75–5.48	0.001	1.13
IWC	9	4.9–14.41	<0.001	4.83	2.41–9.7	<0.001	1.58
Constant	—	—	—	0.12		<0.001	−2.12

	BMI					
Normal	Overweight	Obesity	AN[b]	IWC	Probability[c]	
✓					11%	
✓			✓		27%	
✓				✓	37%	
✓			✓	✓	64%	
	✓				17%	
	✓		✓		39%	
	✓			✓	50%	
	✓		✓	✓	76%	
		✓			21%	
		✓	✓		39%	
		✓		✓	56%	
		✓	✓	✓	80%	

Abbreviations: OW, Overweight; OB, Obesity; AN, Acanthosis Nigricans; IWC, Increased Waist Circumference; OR, Odds Ratio; β, Coefficent β, Prob, Probability.
[a]Variables included in the multivariate analysis are normal weight, overweight, obesity, AN (Acanthosis Nigricans present in the knuckles) and IWC (Increased Waist Circumference).
[b]AN: Acanthosis Nigricans present in the knuckles. Includes Acanthosis Nigricans Groups 1 and 2.
[c]Probability of a HOMA-IR > 2.5.

They recommend just examining the neck when a clinician is looking for AN.[16] In our study, however, AN in the knuckles alone occurred in almost half of the cases (AN1, 68 out of 149). Other studies have also shown that there are many cases with AN in the knuckles without AN in the neck or other classical sites.[17,24-26] Consequently, AN in the knuckles should be considered as a classic, highly prevalent, difficult-to-hide clinical sign that arises a caution of compensatory hyperinsulinemia secondary to IR.

Most AN publications in the last 2 decades focused on two main points: case reports of young subjects with severe AN, typically in quite obese individuals, associated to very high insulin values or retrospective studies designed to identify the prevalence of AN or validate its link to IR.[14,22,27-30] There is a paucity of evidence, however, on the clinical epidemiology of AN. For example, AN prevalence among different BMI or age ranges, different anatomical sites, subjects with 1 or 2 skin phototypes, varieties of clinical expression in these two phototypes, and as a diagnostic tool beyond the link to hyperinsulinemia in overweight or obese subjects. The clinical value of AN in the knuckles in our study could be addressed with two aims: as an easy and costless diagnostic tool suggesting hyperinsulinemia due to IR; and as an early warning marker of IR even in the absence of obesity or overweight. In our study, subjects with a normal BMI and AN in the knuckles had a significantly elevated HOMA-IR index and mean baseline insulin, indicating that hyperinsulinemia due to IR is surely occurring before the BMI increase. This speculation could propose that hyperinsulinemia secondary to IR is an earlier phenomenon, not the consequence, of weight gain. Once overweight or obesity takes place, they potentiate hyperinsulinemia and weight increase. In fact, some authors have proposed obesity as a state of primary insulin hypersecretion leading to obesity.[31,32] Management interventions able to modify insulin action could be addressed to prove whether hyperinsulinemia is the effect or the origin of weight increase and to assess prevention or delay of the clinical consequences of chronic hyperinsulinemia due to IR.

There are many available methods to assess insulin sensitivity.[33,34] The euglucemic hyperinsulinemic clamp and the frequently-sampled intravenous glucose tolerance test are the worldwide-accepted gold standards.[33,35] Their complexity, availability and cost, however, make them not ideal in many clinical scenarios.[33] Although with some well-recognized limitations, most current publications suggest the HOMA-IR index to classify IR.[36,37] Studies in adults have defined a value ≥ 2.5 as the cut-off for IR.[38-40] Studies in different geographic populations, however, have proposed a higher or lower cut-off.[41] In order to allow comparisons with other regions with the most accepted normal value and, in keeping with a similar value proposed in a previous study in our country, we used a value of 2.5.[39] With this value, we found a significant difference in HOMA-IR index and mean fasting insulin between AN cases and controls and between case groups within different BMI, excluding BMI as a confounder. Studies in very young participants with variable BMI and AN in the knuckles should be carried out to find whether comparative higher insulin values occur even earlier. In this study, mean fasting insulin values were higher in AN1 cases than controls but lower than AN2. This feature may suggest that AN in the knuckles is the first step or a very early clinical sign of IR before occurrence in other anatomical sites. AN in the knuckles alone is a frequent feature in normal BMI subjects. In obese subjects it goes together with AN in many other sites.

The great challenge in the obesity and diabetes epidemic is the prevention of these disorders and closely related conditions.[1,42] Any early risk-prediction marker that identifies these populations would be helpful to prevent the whole spectrum of both medical conditions. IR is a biochemical abnormality associated to these since the first stages in its pathogenesis.[3,43] AN, a clinical expression of hyperinsulinemia due to IR, could be an early-in-life diagnostic tool to predict clinical and metabolic expression of IR. In this study, normal BMI subjects with AN in the knuckles and IWC had a 2 out of 3 probability of IR as evidenced by an elevated HOMA-IR index; this increased to 3 out of 4 when overweight was used. This probability is clearly superior than isolated AN (27 and 39%) in the knuckles or IWC (37 and 50%) in normal and overweight participants, respectively. AN in the knuckles increases the power of IWC to select cases with IR by HOMA-IR index even in normal BMI subjects. The few studies of AN carried out in children or young participants, however, have not considered the knuckles as a site for investigation.[13,16,18,44] They have neither studied the diagnostic performance of AN to predict IR by HOMA-IR index.

Our study has some limitations. Firstly, skin phototype of most of the participants was 3 or 4; studies of other phototypes need to be carried out and our findings applied to these skin phototypes. Obesity and diabetes, however, are growing in regions with predominance in phototypes 3 and 4. Secondly, IR was classified on the basis of HOMA-IR index, instead of the euglycemic hyperinsulinemic clamp. It is clear that the cost and difficulties to carry out this technique were the reasons to select the HOMA-IR index in this large population study. HOMA-IR index, on the other hand, has been accepted as a valuable tool for day-to day clinical practice for insulin action assessment.[39]

In conclusion, this study significantly showed a higher HOMA-IR index and fasting insulin values when cases were contrasted to controls. This significance was sustained even when BMI was obviated as a confounder. The association of AN in the knuckles with IWC improved the accuracy to predict IR in all BMI categories. AN in the knuckles in normal BMI participants with an elevated HOMA-IR index could suggest that hyperinsulinemia is not a consequence of obesity but is involved since its inception. Studies of AN in the knuckles should be carried out at an earlier age to define age of appearance; earlier interventions in IR could be valuable to reduce the burden of the disease on public health. Later in life, all interventions to manage obesity and its complications are expensive and relatively inefficient.[48,49]

4. Materials and methods

4.1. Subjects

Three hundred and forty men or women, first- to fourth-year medical students, between 18 and 23 years of age, were randomly and consecutively enrolled. Approval from the Institutional Review Board and written informed consent from all participants were obtained. Five declined to participate and sixteen were excluded due to medical history of prediabetes, diabetes, use of drugs able to modify insulin action and/or secretion or a 10% or greater change in body weight within the last year. Finally, a total of 319 subjects were evaluated. Cases were participants with AN in the knuckles. To analyze a secondary endpoint, there were two groups: those with AN in the knuckles alone (AN1) and those with AN in the knuckles and in other classical sites (AN2). Controls were defined as participants without AN in the knuckles and other classical

sites. Participants without AN in the knuckles but present in any other classical site were classified as AN3. These were not considered cases, since AN in the knuckles was negative, nor controls, since AN was positive in classical sites; therefore, they were excluded for the primary endpoint assessment but contrasted with AN1 and AN2 in some secondary endpoints.

4.2. Study protocol

All participants underwent a medical history with emphasis on personal and family history of components of metabolic syndrome, drug use, anthropometry, blood pressure, skin phototype, and AN assessment in the neck, axillae, elbows and knuckles as recommended.[24] A fasting blood sample was taken for plasma glucose and serum insulin levels to determine HOMA-IR index.[45] Also, a standardized close-up photography of the neck, axillae, elbows, and knuckles was taken.

4.3. Measurements

BMI was obtained and participants were classified into three categories: normal (18–24.9), overweight (25–29.9) and obese ($\geq$30). Increased waist circumference was a value >90 cm in men and >80 cm in women.[46] Three independent blinded observers assessed AN in all participants in the neck, axillae, elbows and knuckles (GGS, MGF, AMTA). Skin phototype was determined as recommended.[47] For fasting plasma glucose, the glucose oxidase method (Stat-Fax Spectrophotometer, Awareness Technology, Palm City Fl., intraassay CV 1.4%, interassay CV 0.6%) was used. For fasting serum insulin determinations an electrochemiluminescence immunoassay (Hitachi-Cobas e411, Roche, Mannheim, Germany, intrassay CV $\leq$2%) was used. HOMA-IR index was calculated as recommended.[45]

4.4. Statistical analysis

Statistical analyses were done using SPSS version 20.0 (IBM Corp. Armonk, NY). Continuous variables are expressed as mean $\pm$ standard deviation; categorical variables are expressed as frequencies. AN proportions between BMI categories were compared using Chi-square test. In quantitative comparative variables Student's t test was performed; one-way ANOVA test was employed when more than two groups were

contrasted. Bonferroni̇́s correction was used as a post-hoc test; distribution of numerical variables was confirmed by Kolmogorov–Smirnov test. A *P* value <.05 was statistically significant. Reliability coefficients for AN assessment were calculated using kappa. Logistic regression was applied in a multivariable analysis to determine correlation with HOMA-IR ≥2.5. Beta factors were implemented to an algorithm to predict the probability of presenting high HOMA-IR values. The sample size was calculated using the means comparison method with a two-sided confidence and power of 95% and 90%, respectively, with an expected mean difference of 1.1 in HOMA values, requiring 143 subjects per group.

Abbreviations

AN	Acanthosis nigricans
AN1	AN in the knuckles alone
AN2	AN in the knuckles and in other classical sites
AN3	Participants without AN in the knuckles but present in any other classical site
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance
IR	Insulin resistance
IWC	Increased waist circumference.
MI	body-mass index

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