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Original

Acanthosis nigricans as an indicator of insulin resistance in Chilean adult population

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Abstract

Background: **Insulin resistance (IR) is associated with a higher risk of multiple diseases and its early detection would allow to minimize the associated risk; the presence of acanthosis nigricans (AN) it's associated to the presence of IR.**

Objective: **To evaluate the sensibility and specificity of AN to diagnose IR in a group of Chilean patients.**

Methods: **We designed a cross-sectional study and it was included subjects that were attended at the Center for the Attention of Metabolic Diseases at the Faculty of Medicine, University of Chile. Sixty subjects (18-60 years age) were included. It was determined BMI and diagnosed AN and skin phototype; blood samples were taken and calculated the HOMA-IR. The normality of the variables where analyzed by Kolmogorov-Smirnov test. There were used χ^2 and the diagnostic concordance between AN and IR was determined using the Kappa index and Pearson's correlation. Sensibility, specificity, positive and negative predictive value were calculated and accepted $p < 0.05$.**

Results: **The IR diagnose was 67% and AN was 43%. The major proportion of subjects diagnosed as positive for IR were also positive for AN (84.6%). The sensibility of AN to find IR was an 84% and specificity was 100%. Positive and negative predictive values were 100% and 89% respectively. It was observed a positive association between BMI and HOMA-IR ($r = 0.674$; $r^2 = 0.454$; $p < 0.001$).**

Conclusion: **To detect acanthosis nigricans in Chilean population may be effective for the early diagnose of insulin resistance and, therefore, reduce the associated cost of the late treatment of glucose metabolic disturbances.**

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Key words: *Acanthosis nigricans. Insulin resistance. Sensibility. Specificity. Chilean adults.*

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ACANTOSIS NIGRICANS COMO UN INDICADOR DE INSULINORESISTENCIA EN POBLACIÓN CHILENA ADULTA

Resumen

Introducción: **La presencia de resistencia a la insulina (RI) se asocia a un mayor riesgo de padecer diversas enfermedades y su detección precoz permitiría minimizar el riesgo asociado; la presencia de acantosis nigricans (AN) se asocia a la presencia de RI.**

Objetivo: **Evaluar la sensibilidad y especificidad de la AN para diagnosticar RI en un grupo de pacientes chilenos.**

Método: **Se realizó un estudio transversal y fueron incluidos sujetos atendidos por el Centro para Atención de Enfermedades Metabólicas, Facultad de Medicina, Universidad de Chile. En sesenta sujetos (18-60 años) fueron determinados IMC, presencia de AN y fototipo de piel; muestras de plasma fueron tomadas para el cálculo del índice HOMA-IR. Fue analizada la normalidad de las variables con el test de Kolmogorov-Smirnov y utilizado χ^2; la concordancia diagnóstica entre AN y RI fue determinada con índice Kappa y correlación de Pearson. Fueron calculados sensibilidad, especificidad, valor predictivo positivo y negativo y aceptado un $p < 0,05$.**

Resultados: **El diagnóstico de RI fue de 67% y AN 43%. La mayor proporción de los sujetos positivos para RI también lo fueron para AN. La sensibilidad de AN para el diagnóstico de RI fue de 84% y la especificidad 100%. Los valores predictivos positivo y negativo fueron 100% y 89% respectivamente. Existe una asociación positiva entre el IMC y el HOMA-IR ($r = 0,674$; $r^2 = 0,454$; $p < 0,001$).**

Conclusión: **En población adulta chilena la presencia de acantosis nigricans puede ser efectivo para un diagnóstico temprano de resistencia insulínica con disminución del costo asociado al tratamiento de las alteraciones en el metabolismo de la glucosa.**

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Palabras clave: *Acantosis nigricans. Resistencia a la insulina. Sensibilidad. Especificidad. Adultos chilenos.*

Abbreviations

AN: Acanthosis nigricans.
IR: Insulin resistance

Introduction

The prevalence of obesity has increased in a considerable way in most developed and developing countries.[1-6] In Chile, 61% of the population over 17 years of age has overweight or obesity. This increase has brought as consequence an increased number of people affected by insulin resistance (IR), hypertension, dyslipidemia and other chronic non transmittable diseases.[7-9] Today, IR is considered a common factor in the development of several conditions of cardiovascular risk and other pathological entities, among them the metabolic syndrome, polycystic ovary syndrome, hypertension, glucose intolerance, type 2 diabetes mellitus, and non alcoholic hepatic steatosis.[10-12] Therefore, it is necessary to find a simple method of easy application in clinical practice, to evaluate the presence of this condition.

The euglicemic *clamp* is considered the gold standard to measure *in vivo* insulin action. However, it's not feasible to apply in a routine way in clinical practice, because it implies to provide a greater number of instrumental equipment and capacitated personal. In counterpart, we counted with mathematical model denominated *homeostasis model assessment* (HOMA), that allows to make insulin resistance estimates (HOMA-IR) and beta cell's function (HOMA-b) using glucose and insulin plasmatic concentrations during fasting hours. This method has showed to have a good concordance with *clamp*.[13-15] Another IR marker that has been proposed to be used in clinical practice is the presence of acanthosis nigricans (AN). AN is a type of dermatoses characterized by hyperpigmentation and thickening of the skin with a velvety look.[16] It's presented in flexion and epidermal attrition areas such as axilla, groin, anterior ulnar zone, popliteal cavity, umbilical area and posterior and lateral region of the neck. Therefore, the observation of these dermatoses would help to diagnose IR. However, AN can be observed in some ethnic populations such as Hispanics, African-Americans an Native-Americans in absence of IR,[17] and that could lower its specificity as a diagnose method.

Considering the elevated prevalence of obesity in Chile and in consequence the high IR risk, it's important to detect the primary clinical signs of the disease. The objective of this present study was to evaluate the sensibility and specificity of AN to diagnose IR in a group of Chilean patients of hispanic origins.

Methodology

Study design and selection of the subjects. We designed a retrospective cross-sectional study. Were included subjects between 18 and 60 years of age that consulted in a spontaneous way or by medical derivation to the attention service executed at the CAMD (Center for the Attention of Metabolic Diseases at the Medicine Faculty of the University of Chile) between January 2006 and August 2008. The exclusion criteria were history of diabetes mellitus diagnosed by a physician and fasting plasma glucose > 99 mg/dl. Procedures executed in the study were in accordance with the Helsinki protocol.[18] A sample size of a minimum of 16 subjects with phototype I and II (table I) and 40 subjects in the group of phototype III and IV were calculated (table I).

Insulin Resistance (IR). Diagnose of IR was made with the HOMA-IR index. The glycemia and insulinemia blood samples were taken during fasting hours and the HOMA-IR index was estimated according to the equation: fasting glycemia (mg/dL)* fasting insulinemia (μUI/mL)/405. The IR cutoff adopted to diagnose of IR was HOMA-IR over 2.5 (mean plus one standard deviation according to the normal distribution on the Chilean population).[19]

Determination of the skin phototype. For the classification of the skin phototype the methodology proposed by Fitzpatrick was executed[20] (table I). The information was collected by a doctor trained through the clinical exam.

Acanthosis Nigricans (AN). The diagnostic of AN was made by a doctor through the direct observation of the cervical region of the studied patients. The result was categorized as presence or absence of AN.

Table I
Classification of skin phototype according to Fitzpatrick T.[20]

Phototype	*Skin type*	*Tan*	*Burns*	*Individual groups, ethnicity*
I	Very white	No	Always	Red hair, freckled, basques
II	White	Minimum	Very easily	European nordic and central european
III	Slightly brown	Gradual	Easily	Blonde hair/brunette
IV	Brown	Yes	Occasionally	Latin
V	Brown to black	Intense and fast	Rarely	Arab, asian, indians
VI	Black	Maximum	Never	Black

Table II
General characterization of the studied group

Variable	*Results Median (intercuartile range)*
Age, years	28.0 (22.0-34.8)
Body weight (kg)	68.0 (60.2-80.2)
Height (mt)	1.6 (1.54-1.67)
Waist circumference (cm)	87.7 (80.4-91.5)
BMI (kg/m^2)	25.2 (22.0-32.0)
Fasting plasma glucose (mg/dL)	81.0 (71.9-90.3)
Fasting plasma insulin (μU/mL)	6.48 (3.96-17.7)
HOMA-IR	1.3 (0.7-3.45)

Anthropometry. Weight was measured with minimal clothing and barefoot, using a digital scale (Seca®, Vogel & Halke GMBH & Co, Germany) with precision of 100 g. Height was obtained using a metallic measuring rod adhered to the Seca scale, with a precision of 1mm. BMI was calculated.

Statistical Analysis. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. The χ^2 test was used for the categorical variables. The diagnostic concordance between AN and IR was analyzed using the Kappa index and Pearson's correlation. Sensibility, specificity, positive predictive value and negative predictive value were calculated. SPPSS software was used (SPSS for Windows. Version 11.5.1, 2002, SPSS Inc.) and it was accepted as significant a $p < 0.05$.

Results

A group of 60 subjects attended at the CAMD (18-62 years old) was studied and most of them where women (83.3%). Fifty percent of subjects presented skin phototype characterized as slightly brown skin (type III) and 20.0% presented skin phototype characterized as brown skin (type IV). The phototypes I was 1.7% and the phototype II was 28.3%. For analysis purposes there were formed two groups: phototype I plus II and phototype III plus IV.

General characteristics of the studied group are presented in table II. A major proportion presents weight excess. According to BMI, overweight and obesity prevalences were 20% and 35%, respectively. Only 45% of the studied group presented a normal nutritional status. Insulin resistance and AN were present in 67% and 43% of subjects, respectively.

To analyzing the relation between the AN and IR diagnose in the studied groups (table III), it can be observed that the major proportion of subjects diagnosed as positive for IR were also positive for AN (84.6%). The sensibility of AN to detect IR was 84% and the specificity was 100%. The positive and negative predictive values were of 100% and 89%, respectively.

Table III
Distribution of the diagnosed cases with insulin resistance and acanthosis nigricans in the studied group

Insulin resistance	*Acanthosis nigricans*		*Total n (%)*
	Positive n (%)	*Negative n (%)*	
Positive n (%)	22 (84.6)	0 (0)	22 (36.7)
Negative n (%)	4 (15.4)	34 (100)	38 (63.3)
Total n (%)	26 (100)	34 (100)	60 (100)

χ^2: 45.425 (p: 0.000); R: 0.87 (p: 0.000); κ: 0.862 (p: 0.000).

For groups I and II the sensibility and specificity were of 100%. In the groups III and IV, the sensibility found was of a 75% and the specificity was of a 100%. In the univariate analysis (lineal regression) in which there was evaluated the association between BMI and HOMA-IR index, the results demonstrated a positive and significant association ($r = 0.674$; $r^2 = 0.454$; $p < 0.001$).

Discussion

In this study we conclude that, in Chilean population with Hispanic origins, the AN diagnosis is a good predictor of insulin resistance (IR). Several authors have indicated that obesity increases the risk of insulin resistance and type 2 diabetes mellitus.[9,21] In the development of IR, the metabolism of the adipose tissue is intrinsically linked and the principal factors that influence this relationship are production of pro-inflammatory cytokines, presence of free non-esterified fatty acids and others that implies a fundamental role in the development of the pathology.[22]

The early identification of patients with IR represents an important action in the public health system, because its evolution towards diabetes mellitus in subjects with familiar predisposition[23] implies among other factors an elevated cost for both health services and society. There is no consensus about the best method to diagnose IR in the general population. Some authors consider that the use of fasting insulin levels is a good predictor of insulin resistance in the normoglycemic subjects compared wiht HOMA index or insulin-to-glucose index.[24,25] Bonora et al. (1998) proposes the utilization of HOMA-IR to indicate IR. The cutoff established to diagnose IR at the Bruneck Study was the HOMA-IR value equal to or higher than the lower limits of the top quintile distribution values in normal metabolic subjects (HOMA-IR ≥ 2.7). Similar values of HOMA-IR cutoff was adopted by other studies according the distribution of non diabetic population.[27-29] In the current study we used the cutoff proposed for Chilean non obese individuals (2.5) and it's based on the mean plus one standard deviation (19).

Table IV
Distribution of the diagnosed cases with insulin resistance and acanthosis nigricans in groups with skin phototype according to Fitzpatrick I and II

Insulin resistance	Acanthosis nigricans		Total n (%)
	Positive n (%)	Negative n (%)	
Positive n (%)	10 (100)	0 (100)	10 (55.6)
Negative n (%)	0 (100)	8 (100)	8 (44.4)
Total n (%)	10 (100)	8 (100)	18 (100)

χ^2: 18.0 (p: 0.000); R: 1.0 (p: 0.000); κ: 1.0 (p: 0.000).

Table IV
Distribution of the diagnosed cases of insulin resistance and acanthosis nigricans in groups with skin phototype according to Fitzpatrick III and IV

Insulin resistance	Acanthosis nigricans		Total n (%)
	Positive n (%)	Negative n (%)	
Positive n (%)	12 (75.9)	0 (0)	12 (28.6)
Negative n (%)	4 (25.0)	26 (100)	30 (71.4)
Total n (%)	16 (100)	26 (100)	42 (100)

χ^2: 27.3 (p: 0.000); R: 0.8 (p: 0.000); κ: 0.788 (p: 0.000).

Many studies have corroborated that AN is manifested with greater intensity in black populations or individuals with Hispanic or Latin origins.[30-31] In school Korean kids AN is present in 8.4% of the males and 5.1% of the females, being proportional to the BMI and the percentage of body fat, and in young Australian aboriginal population the presence of AN is a 43%. In the adult Chilean population it is not described the prevalence of AN and only in a study made in school kids with hyperglycemia the prevalence was greater than levels founded in euglycemic school kids (9.5 y 0.6% respectively, $p < 0.001$).[32]

The etiology of AN is related to different syndromes, the majority of them are genetic. AN is related to the insulin resistance syndrome and it's associated to mutations and primary defects in the insulin receptor and in PPARγ.[33] This nuclear receptor has an important role in the adipogenesis process, acting also as a receptor for pharmaceuticals compounds that enhance insulin sensibility such as thiazolidinediones.[34]

The increase of the insulin plasmatic concentrations, characteristic of the insulin resistance syndrome, results in an over stimulation of the family of receptors that belong to the IGF (insulin growth factor), mainly the IGF1, which are similar to the insulin receptors. Major IGF1 exposition in dermis' fibroblasts and keratinocytes stimulates its proliferation causing the clinical signs of AN.[35] The proposed mechanism for the activations of IGFR1 (member of tyrosine kinase receptor super family) involves a dimerazation of the receptor by activation of the ligand and self phosphorylation of the tyrosine residues in the cytoplasmic domains. This generates a conformational change in the domains and its consequent activation of signal pathways as the ras/MAPK/ERK, PI3K and AKT and phospholipase C-g pathways.[35]

Analyzing the phototype I and II and phototype III and IV groups, the results of our study confirm the potency of the relation between the presence of AN and IR in this group of patients, as it can be observed in tables IV and V. The diagnostic tests applied (table IV) indicate a good discrimination capacity principally in subjects with skin phototype I and II, although good values were also observed in the group with skin phototype III and IV.

Our results agree with the results founded by other authors,[30] and indicates that there was a strong association between diagnose of IR and the presence of AN in the studied population, which is represented by the elevated values founded in the specificity and sensibility tests, as in the positive and negative predictive values. Some of the limitations of this study are the impossibility to analyze other biochemical parameters like lipids profile and this relationship with IR and AN. Also, it was not included a 2-h oral glucose tolerance test in the medical examination aimed to detect impaired glucose tolerance. In addition, there is a lower calibration between sexes in the sample, prevailing women.

Conclusions

According our results, it can be concluded that AN diagnose in Chilean population may be an effective tool for the early diagnose of IR. Our future studies will be focus in the enlargement of the study group, searching for the association between different age ranges and increasing the group of subjects that belong to skin phototype I and II and that also belong to the masculine gender.

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