

Relation Between Acanthosis Nigricans and Insulin Sensitivity in Overweight Hispanic Children at Risk for Type 2 Diabetes

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OBJECTIVE— To investigate in a population of Hispanic children if 1) the presence of acanthosis nigricans (AN) is related to insulin sensitivity (S_i) independent of adiposity and 2) scale scoring AN severity adds to the clinical estimation of insulin sensitivity, above and beyond the presence or absence AN alone.

RESEARCH DESIGN AND METHODS— The study population, 131 Hispanic overweight children (mean BMI percentile 97.0 ± 3.1 , 72 boys, 59 girls, ages 8–13 years, mean Tanner stage 2.4 ± 1.5) with a family history of type 2 diabetes, underwent a physical examination of the neck to determine AN absence or presence (0–1), AN extent score (0–4 scale), AN texture score (0–3 scale), and an AN combined score (extent + texture; 0–7 scale). S_i was measured by the frequently sampled intravenous glucose tolerance test and minimal modeling. Multivariate linear regression analysis was used to determine the role of BMI and AN in predicting S_i .

RESULTS— BMI was the main predictor of S_i , explaining ~41% of the variance. The presence of AN explained an additional 4% of the variability in S_i ; scale scoring of AN extent or texture did not significantly improve the prediction.

CONCLUSIONS— Although AN is an independent risk factor for insulin resistance in overweight Hispanic children at risk for type 2 diabetes, body adiposity is the primary determinant of insulin sensitivity. In addition, scale scoring AN seems of minimal usefulness in clinically estimating the severity of insulin resistance over and above assessing the presence or absence of AN and calculating BMI.

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With the rise of overweight (1) and type 2 diabetes (2,3) in the pediatric population, especially in young Hispanics and other minority groups, early identification of those at el-

evated health risk is important so that appropriate interventions can be established. Insulin resistance is thought to be a major factor in the pathophysiology of type 2 diabetes in both adults and chil-

dren (4–6). Acanthosis nigricans (AN), a skin disorder characterized by hyperpigmentation, hyperkeratosis, and papillomatosis, is a clinical marker that has been linked to surrogate markers of insulin resistance in adults (7,8) and adolescents (9), but only a few studies have explored the relation between directly measured insulin sensitivity (S_i) and AN in children (10–12). Studies in adults have suggested that those with AN have elevated fasting insulin levels (13,14). However, these studies were limited in that they did not measure S_i directly, neither did they evaluate the severity of AN. Burke et al. (8) proposed a classification system to grade the severity of AN and found that the severity of AN was associated with elevated fasting insulin and increased BMI. Previous studies that have examined the relation between S_i and the severity of AN in adults and children have found mixed results (10–12). Thus, the interrelation between obesity, insulin resistance, and severity of AN still needs to be clarified, particularly in children at risk for diabetes.

Therefore, in this population of Hispanic children at risk of developing type 2 diabetes, our objectives were to 1) determine if the presence of AN was related to S_i independent of adiposity and 2) ascertain if scale scoring AN severity added to the clinical estimation of S_i above and beyond the presence or absence of AN alone.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— The study population of 131 children (72 boys and 59 girls) was recruited through the Study of Latino Adolescents at Risk for Type 2 Diabetes (an ongoing longitudinal study of the pathophysiology of type 2 diabetes in Latino youth). The subjects were screened to meet the following inclusion criteria: 1) Hispanic origin (both sets of grandparents reported to be Hispanic), 2) a positive family history (sibling, parent, or grand-

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Abbreviations: AN, acanthosis nigricans; DEXA, dual-energy X-ray absorptiometry.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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parent) for type 2 diabetes, 3) age 8–13 years, 4) BMI \geq 85th percentile for age and sex according to the Centers for Disease Control and Prevention growth charts (15), and 5) absence of diabetes, as established by an oral glucose tolerance test and according to Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus diagnosis criteria (16,17). Children were excluded if they were taking medications known to affect insulin resistance or body composition or had been diagnosed with any major illness since birth. The subjects were recruited from greater Los Angeles County, California, through a combination of medical referrals (Los Angeles County) and University of Southern California [USC] Pediatric Diabetes Prevention Clinic and other local physicians), local advertisements, local health fairs, and word of mouth. The subjects were of Mexican-American and Central-American heritage. The Institutional Review Board of the Health Sciences Campus, USC, approved the study. Informed consent was obtained from all parents and assent was obtained from all children after the nature of the procedures was explained and before testing commenced.

Subjects arrived at the USC General Clinical Research Center at \sim 0800 after an overnight fast for the outpatient visit. The subjects underwent a comprehensive physical examination, which included Tanner staging (18,19), anthropometric measurements (height and weight were recorded to the nearest 0.1 cm and 0.1 kg, respectively), and neck examination for the absence or presence of AN.

Subjects were admitted to the research center in the afternoon 1–2 weeks after the outpatient visit. A whole-body dual-energy X-ray absorptiometry (DEXA) scan was performed to determine whole-body composition using a Hologic QDR 4500W. The subjects were given dinner and an evening snack, with all food being consumed before 2000. Only water could be consumed between 2000 and testing the following morning.

Determination of AN neck severity

AN of the neck was assessed in all subjects by a single trained clinician (M.J.W.) as part of the comprehensive physical examination. The neck alone was used because of ease of access and higher reproducibility and because the neck is always involved when other areas are affected (20).

If AN was present, it was scored using the Burke neck AN scoring methods (8). AN severity was thus expressed by four separate scoring scales: AN dichotomous score (absent/present), AN extent score (0–4 scale), AN texture score (0–3 scale), and AN combined score (extent + texture; 0–7 scale). The AN combined scale represents the simple sum of the Burke scores for AN extent and AN texture.

Insulin-modified frequently sampled intravenous glucose tolerance test

At \sim 0630, a topical anesthetic (EMLA cream; AstraZeneca, Wilmington, DE) was applied under occlusion to the anteorbital fossa of both arms; flexible intravenous catheters were then placed in both arms at \sim 0730. Two fasting blood samples were drawn at -15 and -5 min for determination of basal glucose and insulin. At $t = 0$, glucose (25% dextrose, 0.3 g/kg body wt) was administered intravenously over 1 min in one arm, and blood samples from the contralateral arm were collected at the following time points: 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin (0.02 units/kg body wt; Humulin R regular insulin for human injection; Eli Lilly, Indianapolis, IN) was injected intravenously at 20 min. Plasma was analyzed for glucose and insulin, and values were entered into the MINMOD MILLENIUM 2003 computer program (version 5.16; Richard N. Bergman) for determination of S_i and the acute insulin response (21,22). Insulin was assayed in duplicate with a specific human insulin enzyme-linked immunosorbent assay kit from Linco (St. Charles, MO). The insulin interassay coefficients of variation from our laboratory are 7–10%; the insulin intra-assay coefficient of variation is $<2\%$. Glucose was measured in duplicate using a YSI 2700 Analyzer (YSI, Yellow Springs, OH).

Statistical analysis

Sex differences in metabolic and physical characteristics were explored using independent samples t tests. Spearman correlations were used to identify associations among S_i , anthropometric and body composition variables, and the four AN scoring scales. Because S_i data were not normally distributed, this variable underwent log transformation before being entered as the dependent variable into the regression models. Multivariate regression analysis was used to determine

which measure of AN explained the most variance in S_i , independent of body composition, age, and sex. In models 1–5, the log-transformed S_i was entered as the dependent variable and sex, Tanner stage and BMI were included as the independent variables. In addition, models 2–5 included the following measures of acanthosis: AN dichotomous, AN extent, AN texture, and AN combined, respectively. $P < 0.05$ was considered to be significant. Statistical analysis of the data was performed using Statistical Packages for Social Sciences (SPSS) version 11 and EpiInfo software (version 6.0; Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Physical and metabolic characteristics of subjects

The physical and metabolic characteristics of the children in this study are presented in Table 1. There were no significant physical or metabolic differences across sex, except that girls tended to be of a higher Tanner stage compared with boys ($P < 0.01$). Within this sample, 96 of 131 (73%) subjects had AN. Those with AN subsequently underwent severity scoring as described in RESEARCH DESIGN AND METHODS. All AN measures correlated negatively with S_i (correlation coefficients -0.45 to 0.61 ; $P < 0.01$) and positively with all measures of body composition (correlation coefficients 0.478 – 0.750 ; $P < 0.01$) (Table 2).

Multiple linear regression analysis to establish the contribution of AN measures to S_i independent of BMI

Multivariate linear regression analysis showed that BMI was significantly ($P < 0.001$) and negatively related to S_i after adjustment for sex and Tanner stage and, all together, contributed $\sim 41\%$ of the variance in S_i (model 1, $r^2 = 0.41$) (Table 3). When this same regression was calculated to include AN as a dichotomous variable, the model explained 44.6% of the variance in S_i (Model 2). However, when AN was entered into the regression model without BMI, it could explain only 24.1% of the variance in S_i . When the remaining AN scales were substituted for the AN dichotomous scale, the models explained 46.3–47.3% of the variance in S_i (models 3–5). All AN measures were negatively and significantly related to S_i and

Table 1—Physical and metabolic characteristics of subjects

	Boys	Girls	Total
n	72	59	131
Age (years)	11.3 ± 1.6	11.0 ± 1.7	11.1 ± 1.7
Height (cm)	151.0 ± 10.8	149.2 ± 12.3	150.2 ± 11.5
Weight (kg)	64.7 ± 17.2	66.1 ± 23.0	65.3 ± 19.9
Tanner stage*	1.9 ± 1.3	3.0 ± 1.4	2.4 ± 1.5
BMI (kg/m ²)	28.0 ± 4.9	28.8 ± 6.1	28.4 ± 5.5
BMI percentile	97.0 ± 3.1	96.7 ± 3.1	96.9 ± 3.1
Total fat mass (kg)	23.4 ± 8.9	26.6 ± 8.8	24.8 ± 10.3
Total lean tissue mass (kg)	39.0 ± 10.1	37.0 ± 11.2	38.0 ± 10.6
Fasting glucose (mg/dl)	93.9 ± 6.3	93.0 ± 5.7	93.4 ± 6.0
2-h glucose (mg/dl)	124.2 ± 18.9	123.2 ± 15.9	123.8 ± 17.6
Fasting insulin (μU/ml)	18.2 ± 11.3	21.9 ± 14.9	19.9 ± 13.1
Insulin sensitivity (×10 ⁻⁴ min · μU ⁻¹ · ml ⁻¹)	1.9 ± 1.1	2.0 ± 1.4	1.9 ± 1.3
AN dichotomous (absent/present) [%]	21/51 (70.8)	14/45 (76.3)	35/96 (73.3)
AN neck texture (0–3)	0.7 ± 1.0	1.2 ± 1.2	1.0 ± 1.1
AN neck extent (0–4)	2.0 ± 1.6	2.3 ± 1.7	2.2 ± 1.6
AN combined (0–7)	2.6 ± 2.4	3.5 ± 2.7	3.0 ± 2.6

Data are means ± SD unless otherwise noted. *Tanner stage of boys vs. girls, $P < 0.01$.

independent of BMI (models 2–5) (Table 3). Results were not appreciably different if total fat and total lean tissue mass measured via DEXA were included as body composition variables in place of BMI (data not shown).

CONCLUSIONS— The major finding of this study was that although AN was indeed a statistically significant contributor to S_i independent of BMI, its contribution was relatively small and only added ~4–6% to the overall variance in S_i . Scale scoring of AN severity yielded little additional clinically relevant information beyond the simple determination of the presence or absence of AN. Thus, body adiposity rather than AN appeared to be the primary determinant of variance in insulin resistance in this population.

Our study differed from previous studies that have explored the relation between AN and insulin resistance in a number of ways. First, we used a direct measure of whole-body S_i rather than fasting insulin. Second, we determined whether the severity of AN was more strongly related to insulin resistance. Third, we studied a population of Hispanic youth at high risk for developing type 2 diabetes. Previous studies have inferred the relation between insulin resistance and AN through the use of indirect indexes, such as fasting insulin (7–9,23–27). The studies that have used direct

measures of S_i compared with AN include one in girls with premature adrenarche (10) and another in women with hyperandrogenism (12). These studies examined the effect of androgen excess and AN on S_i . Both found that subjects with AN had decreased S_i levels that were independent of adiposity. These studies were limited by their small sample sizes (12 and 11 subjects, respectively) and did not address AN severity. Nguyen et al. (11) examined S_i in overweight children with AN and found that AN correlated with decreased S_i , but after adjusting for BMI, this association was no longer significant. However, Nguyen et al. did not stratify the subjects by AN severity; if they had, it could have unmasked a subtle contribution of AN to S_i that would otherwise have been obscured by the very large effect of adiposity. Our study attempted to address the limitations of previous studies

while focusing on a much understudied segment of the population, overweight Hispanic adolescents.

Our analysis showed that AN was inversely related to directly measured S_i independent of adiposity. Although body composition was found to be the strongest predictive variable of S_i , the presence of AN was indicative of modestly greater insulin resistance as compared with subjects who did not have the skin pathology. Because AN and S_i were both strongly related to BMI, it is important to consider more specific measures of body fat. In the current study, we were able to examine whether a convenient clinical indicator of adiposity (BMI) provided similar results to a more sophisticated research measure of body fat (DEXA). Our data showed that the relation between AN and S_i independent of adiposity was very similar, even when the more sophisticated measures of body composition were used in the analysis.

An assessment of whether grading of AN severity adds to the clinical estimation of S_i is important to determine if the added time and effort required to scale score AN is justified. Although all regression models showed that AN was an independent correlate of S_i beyond that of adiposity, the differences between the various severity scales were minimal. Of the AN severity scoring scales, the combined scale (0–7) had the strongest association with S_i . However, this scale explained only ~3% more variance in S_i than the dichotomous (absent or present) scale. Given the small differences between the regression models, we believe evaluating AN using scale scoring provides little additional clinical benefit in estimating S_i and therefore is unlikely to aid in the medical decision-making process. However, our findings support the American Diabetes Association criteria for screening for type 2 diabetes in children with ele-

Table 2—Correlations among insulin sensitivity, AN scoring scales, and body composition measures

	AN dichotomous	AN extent	AN texture	AN combined	BMI	Total fat mass	Total lean mass
S_i	-0.449	-0.577	-0.586	-0.606	-0.700	-0.678	-0.561
BMI	0.478	0.604	0.602	0.638	—	0.945	0.750
Total fat mass	0.495	0.619	0.631	0.661	0.945	—	0.739
Total lean mass	0.400	0.532	0.557	0.572	0.750	0.739	—

All results are significant at $P < 0.01$.

Table 3—Multiple linear regression to assess the contribution of AN on insulin sensitivity after adjusting for sex, Tanner stage, and BMI

Dependent variable (log insulin sensitivity)	Independent variables	$\beta \pm \text{SEE}$	P
Model 1 $r^2 = 0.410$	Sex	0.05 \pm 0.10	NS
	Tanner stage	-0.05 \pm 0.04	NS
	BMI	-0.08 \pm 0.01	0.001
Model 2 $r^2 = 0.446$	Sex	0.05 \pm 0.10	NS
	Tanner stage	-0.04 \pm 0.04	NS
	BMI	-0.07 \pm 0.01	0.001
Model 3 $r^2 = 0.463$	Dichotomous (0-1)	-0.27 \pm 0.11	0.02
	Sex	0.07 \pm 0.10	NS
	Tanner stage	-0.04 \pm 0.04	NS
	BMI	-0.06 \pm 0.01	0.001
Model 4 $r^2 = 0.467$	Neck extent (0-4)	-0.11 \pm .035	0.002
	Sex	0.10 \pm 0.10	NS
	Tanner stage	-0.02 \pm 0.04	NS
	BMI	-0.06 \pm 0.01	0.001
Model 5 $r^2 = 0.473$	Neck texture (0-3)	-0.18 \pm 0.06	0.001
	Sex	0.09 \pm 0.10	NS
	Tanner stage	-0.03 \pm 0.04	NS
	BMI	-0.05 \pm 0.01	0.001
	Combined scale (0-7)	-0.08 \pm 0.02	0.001

SEE, standard error of the estimate.

vated BMI and the concomitant presence of AN (17).

Our data support previous suggestions that AN is more highly related to increased adiposity than to S_i (11,28). However, the presence of AN was an added, albeit minor, predictor for more severe insulin resistance in these children. Considering the already elevated risk for insulin resistance in overweight children, the associated presence of AN in these individuals heightens the need for immediate screening for type 2 diabetes and for possible interventions to improve S_i .

In conclusion, in overweight Hispanic children at risk for type 2 diabetes, we found that although AN is an independent risk factor for insulin resistance, body adiposity is the primary determinant of S_i . However, given the modest clinical contribution of AN, it should be viewed in the context of overall risk assessment for type 2 diabetes as secondary to body composition. In addition, scale scoring AN seems to be of minimal usefulness in clinically estimating the severity of insulin resistance over and above assessing the presence or absence of AN and calculating BMI.

Although the clinical utility of AN severity as an individual marker of insulin resistance is limited, this measure may yet

have a role in the development of a clinical prediction equation for S_i when used in combination with other independent clinical measures of insulin resistance, such as plasma insulin (29,30). In addition, further longitudinal investigations are needed to ascertain whether such clinical prediction of S_i is truly useful in quantitatively predicting progression to type 2 diabetes.

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