

ASSOCIATION OF ACANTHOSIS NIGRICANS WITH RISK OF DIABETES AND INSULIN RESISTANCE

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Acanthosis nigricans (AN) is associated with a variety of insulin resistance states,^{1,2} and is a reliable predictor of hyperinsulinemia in obese individuals.^{3,4} Since AN is readily visible, it could serve as a marker for insulin resistance in populations with high prevalence of AN and type 2 diabetes mellitus (DM).⁵ In the rapidly modernizing countries of the Arabian Peninsula, there has been increasing concern about the rising prevalence of DM and its impact on health care services.⁶⁻⁹ We evaluated the prevalence of undiagnosed DM and insulin resistance in a group of subjects with AN, in a newly sedentary population of United Arab Emirates (UAE) nationals. In addition, we examined the importance of age, sex, body mass index (BMI) and family history in predicting DM and insulin resistance in subjects with AN.

Patients and Methods

One hundred subjects with AN, with ages ranging between 16 to 65 years, were included in this study. They all presented to the Dermatology clinic of a tertiary hospital in the UAE with various dermatologic complaints over a period of three years. None of the patients, who were all self-referred, was known to have DM, and none was receiving glucocorticoids at the time.

AN was identified on the nape of the neck and other body sites by one of the authors (GGL). The defect consisted of markedly thickened, creased, velvety skin that was dark brown or black in color. The degree of AN severity was not reported. The study was approved by the Ethics Committee and all subjects gave informed consent.

Height and weight were measured in all patients. Family history of DM was assessed in most patients.

Obesity was defined as body mass index (BMI) of ≥ 30 kg/m². A standard (75 g) oral glucose tolerance test (OGTT) was performed according to the WHO recommendations, and blood was sampled for glucose and insulin at 0, 30, 60, and 120 minutes. Severe insulin resistance was defined as fasting serum insulin level above 300 pmol/L, or peak (post-OGTT) insulin levels above 2100 pmol/L. Fasting insulin levels below 180 pmol/L or peak insulin levels below 900 pmol/L were considered to be normal.

Samples for insulin were centrifuged and the serum was stored at -20°C until assay. Serum insulin concentrations were quantitated with a solid-phase ¹²⁵I radioimmunoassay kit (Diagnostic Products, USA). This assay indicated a fasting 2 SD insulin range of 0-180 pmol/L for a nondiabetic subject. The intra- and interassay coefficients of variation were 5% and 10%, respectively. Serum glucose was determined by the glucose dehydrogenase method (Dimension Clinical Chemistry System, Dade International Inc., USA).

Statistical analyses were performed with the use of the Statistical Package for Social Sciences (SPSS) program. Data were presented as the mean \pm SD. Comparison of group means was performed with the use of the Student's *t*-test and the one-way analysis of variance with Duncan's multiple range test. Relationships among variables were studied by linear regression procedures. Maentel-Haenszel procedure was used to calculate the relative risk (RR), and the 95% confidence intervals (CI). Statistical significance was set at a two-tailed probability of $P < 0.05$.

Results

Table 1 shows the results of the OGTT in 100 subjects with AN. Thirteen subjects were considered to have DM,

TABLE 1. Results of oral glucose tolerance test (OGTT).

Fasting serum glucose	≤ 6.0	6.1-6.99	≥ 7.0	Total
2 hr OGTT (mmol/L)				
<7.8	62	4	0	66
7.8-11.0	11	10	2	23
≥ 11.1	1	4	6	11
Total	74	18	8	100

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TABLE 2. Results of OGTT in obese and nonobese subjects.

Variables	Obese (n=51)	Nonobese (n=49)	P-value
BMI (kg/m ²) (mean)	34.3±4.61	25±3.08	<0.0001
IGT (%)	13 (25.5)	12 (24.5)	NS
DM (%)	5 (9.8)	8 (16.3)	NS
Euglycemic (%)	33 (64.7)	29 (59.2)	NS

NS=not significant.

TABLE 3. Relative risk for insulin resistance in obese and nonobese euglycemic subjects (N=62).

Variable	Obese (n=32)	Non-obese (n=30)	Relative (CI) risk
Insulin resistance (%)	22 (68.7)	10 (33.3)	2.06 (1.18-3.60)*
Normal insulin (%)	10 (31.3)	20 (66.7)	

*P<0.006 (very highly significant).

TABLE 4. Characteristics of the subjects grouped by glucose impairment.

Variables	Euglycemic n=62	IGT n=25	DM n=13
Age (years)	28.3±9.6	31±10.2	42.6±8.5*
Males	18 (29%)	4 (16%)	3 (23%)
Females	44 (71%)	21 (84%)	10 (77%)
BMI (kg/m ²)	30.4±5.8	31.8±5.7	31.9±7.4
FH of DM	47 (75.8%)	16 (64%)	8 (62%)
Fasting glucose (mmol/L)	5.3±0.4	5.9±0.6	7.15±0.7*
Fasting insulin (pmol/L)	155.2±86.2	199.9±206.5	136.5±58.5

Plus-minus values are mean ± SD; FH=family history; *P<0.05, versus the other 2 groups.

TABLE 5. Relative risk for abnormal glucose or insulin in all subjects with AN.

Variables	Abnormal glucose or insulin n=70 (%)	Normal glucose or insulin n=30 (%)	Relative risk (RR)	95% confidence interval (CI)
Age (years)				
≤30	26 (37.1)	18 (60.0)	0.76*	0.57-1.00
>30	44 (62.9)	12 (40.0)		
Sex				
Male	19 (27.1)	6 (20.0)	1.12	0.85-1.46
Female	51 (72.9)	24 (80.0)		
BMI (kg/m ²)				
<30	29 (41.4)	20 (66.7)	0.76*	0.59-0.99
≥30	41 (58.6)	10 (33.3)		
FH of DM				
Positive	48 (68.6)	23 (76.7)	0.89	0.69-1.16
Negative	22 (31.4)	7 (23.3)		

*P<0.05 between groups.

based on a 2-hr OGTT serum glucose value of ≥11.1 mmol/L (11 subjects), or a fasting serum glucose value of ≥7 mmol/L (2 subjects). Twenty-one subjects had impaired glucose tolerance (IGT), based on a 2-hr OGTT serum glucose value of 7.8-11 mmol/L. Four additional subjects with fasting serum glucose value of 6.1-6.99 mmol/L were included in the IGT group. Of the remaining 62 (euglycemic) subjects, four (6.4%) had severe, and 28 (45.2%) had mild to moderate insulin resistance.

Most of the subjects were females (75%), and approximately half were obese. Table 2 shows the results of OGTT in obese and nonobese subjects. The proportion of subjects with DM, IGT, or euglycemia was not significantly different between the two groups. Euglycemic subjects who were obese were more likely, however, to have insulin resistance (Table 3).

Table 4 shows the characteristics of all subjects grouped by their glucose tolerance. Subjects with DM were significantly older in age (P<0.05). In addition, there was a trend towards lower fasting insulin levels in subjects with DM, compared with the IGT and euglycemic subjects (P=0.16, and 0.35, respectively). There were no significant differences between the IGT and euglycemic subjects with regards to age, BMI, sex, and family history of DM. However, when subjects were regrouped into those with normal results (n=30), and abnormal results (DM, IGT, and insulin resistance) (n=70), the likelihood of abnormal results was higher in those subjects who were older (age ≥30 years) or obese (BMI ≥30 kg/m²) (Table 5). Multiple regression analysis confirmed these results (data not shown).

Discussion

Although the prevalence of AN in the UAE has not been reported, one of our authors (GGL) has observed it to be quite prevalent in obese UAE nationals. Our results show that the prevalence of undiagnosed DM, glucose intolerance, and insulin resistance is high (70%) in UAE nationals with AN. The main predictor of DM in these subjects was age over 30 years. Unfortunately, we did not study a control group. Thus, the relative risk for undiagnosed DM, IGT, or insulin resistance cannot be determined from this study. In a similar cross-sectional study,¹⁰ Mishal reported a high prevalence of DM in Jordanian subjects with AN at 28.8% in the 15-45-year age group and 90% in those over 45 years. However, the vast majority of his subjects were obese. Although obesity in the absence of AN is a risk factor for glucose intolerance, we believe that obesity was not a major factor in our analysis, as only half of the subjects were obese, and the results of OGTT did not significantly differ whether subjects were obese or not. Although the exact mechanisms responsible

for the development of AN in the context of insulin resistance remain obscure, it is believed that hyperinsulinemia stimulates the growth of keratinocytes and/or dermal fibroblasts, resulting in the development of AN.^{1,11}

Insulin resistance was assessed in our study by measuring baseline fasting insulin levels as well as maximal insulin responses to oral glucose. The results of this test, especially in the absence of hyperglycemia, correlate well with estimates of insulin resistance obtained using a euglycemic clamp.^{12,13} We found that over half of the euglycemic subjects had insulin resistance. This was predominantly of mild to moderate severity, probably reflecting milder forms of AN. As expected, the relative risk for having insulin resistance in euglycemic subjects was higher in those who were obese. Our finding of normal insulin levels in almost half of the euglycemic subjects, however, suggests that other genetic and environmental factors besides insulin resistance could be contributing to the expression of AN.¹⁴ Since all our subjects had AN to start with, it was not possible to evaluate the importance of such factors.

In summary, we found that UAE nationals with AN have high prevalence of undiagnosed DM, glucose intolerance, and insulin resistance. Thus, screening for DM in subjects with AN can help identify individuals with undiagnosed DM who, if untreated, are at high risk of complications. It can also identify individuals with glucose intolerance and insulin resistance who will benefit most from interventions such as weight reduction and regular physical activity.

References

1. Cruz PD Jr, Hud JA Jr. Excess insulin binding to insulin-like growth receptors: proposed mechanisms for acanthosis nigricans. *J Invest Dermatol* 1992;98(Suppl):82S-85S.
2. Flier JS. Metabolic importance of acanthosis nigricans. *Arch Dermatol* 1985;121:193-7.
3. Stuart CA, Pate CJ, Peters EJ. Prevalence of acanthosis nigricans in an unselected population. *Am J Med* 1989;87:269-72.
4. Hud JA Jr., Cohen JB, Wagner JM, Cruz PD Jr. Prevalence and significance of acanthosis nigricans in an adult obese population. *Arch Dermatol* 1992;128:941-4.
5. Stuart CA, Smith MM, Gilkison CR, Shaheb S, Stahn RM. Acanthosis nigricans among Native Americans: an indicator of high diabetes risk. *Am J Public Health* 1994;84:1839-42.
6. Alwan A, King H. Diabetes in the Eastern Mediterranean Region. *World Health Stat Q* 1992;45:355-9.
7. Asfour MG, Lambourne A, Soliman A, et al. High prevalence of diabetes mellitus and impaired glucose tolerance in the Sultanate of Oman. Results of the 1991 National Survey. *Diabet Med* 1995;12:1122-5.
8. Fatani H, Mira SA, El-Zubier AG. Prevalence of diabetes mellitus in rural Saudi Arabia. *Diabet Care* 1987;10:180-3.
9. Omar A, Elsir K, Muneer M, et al. Diabetes mellitus in Al Ain: the impact on hospital services. *Emirates Med J* 1985;3:119-22.
10. Mishal AA. Acanthosis nigricans: a new analysis of associated endocrine and malignant disorders. *Ann Saudi Med* 1997;17:651-3.
11. Schwartz RA. Acanthosis nigricans. *J Am Acad Dermatol* 1994;31:1-19.
12. Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 1994;11:286-92.
13. Vidal-Puig A, Moller DE. Insulin resistance: classification, prevalence, clinical manifestations, and diagnosis. In: Azziz R, Nestler JE, Dewailly D, editors. *Androgen excess disorders in women*. Philadelphia: Lippincott Raven, 1997:227-36.
14. Panidis D, Skiadopoulou S, Rousso D, Ioannides D, Panidou E. Association of acanthosis nigricans with insulin resistance in patients with polycystic ovary syndrome. *Br J Dermatol* 1995;132:936-41.