Acanthosis Nigricans and Oral Glucose Tolerance in Obese Children
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The recent dramatic increase in childhood obesity has been accompanied by an increased incidence of acanthosis nigricans (AN), with reports of up to 62% of obese youth having this condition.1 AN, a dermatologic manifestation characterized by thick and darkened layers of skin, has been proposed as a potentially useful clinical marker of insulin resistance and increased risk of future type 2 diabetes.2,4 This contention is supported by metabolic studies, which have shown that in obese children, AN is significantly associated with hyperinsulinemia, impaired postprandial glucose and insulin responses, and type 2 diabetes.2,4

Because children with AN tend to be at the most severe spectrum of obesity, it is not clear whether AN is independently associated with increased metabolic risk. Indeed, some reports have suggested that AN is not a reliable clinical marker of hyperinsulinemia and insulin resistance when fat mass is taken into account.5–7 Therefore, to address these conflicting reports, we sought to evaluate whether AN, independent of level of adiposity, is associated with increased basal and glucose-stimulated insulin levels in obese children. We hypothesized that obese children with AN would have higher fasting and postprandial levels of insulin compared to obese children without AN.

**Methods**

This study was approved by the University of Minnesota Institutional Review Board. Data were abstracted from the medical charts of 145 obese (body mass index [BMI] >95th percentile for age and gender) children and adolescents (8-17 years old) who were seen in the University of Minnesota Pediatric Weight Management Clinic between 2004 and 2008. Standard oral glucose tolerance test (OGTT) measures were performed in the clinic, which included a baseline blood draw followed by a 75-g glucose load and serial blood samples (for determination of blood glucose and insulin) obtained every 30 minutes for 2 hours. Standard processing and analytic procedures had been used for determination of blood glucose, insulin, lipid profile, liver enzymes, hemoglobin A1C (HbA1c). C-reactive protein (CRP) values were available for most patients but not all were performed with a high-sensitivity assay. Patients were classified by AN status, based on the clinical diagnosis of the condition recorded in the medical chart. Linear regression analysis was used to compare baseline variables between the AN group and non-AN control group adjusting for age, gender, and BMI where appropriate. Repeated measures (30, 60, 90, 120 minutes during OGTT) analysis of covariance was used to compare glucose and insulin levels between groups adjusting for age, gender, and BMI. Statistical analyses were conducted with SPSS (version 16.0, SPSS Inc, Chicago, IL). P values less than .05 were considered statistically significant.

**Results**

Clinical characteristics are shown in Table 1. Of the 145 obese patients, 68 were clinically diagnosed with AN (age 12.4 ± 2.6 years, 48 girls, 20 boys) and 77 did not carry this diagnosis (age 12.4 ± 2.7 years, 38 girls, 39 boys). There were no differences in gender or age between groups. The AN group had significantly higher BMI than the non-AN group. There were no differences between groups for systolic or diastolic blood pressure, high-density lipoprotein (HDL) cholesterol, triglycerides, very low density lipoprotein (VLDL) cholesterol, or aspartate aminotransferase (AST). Although not statistically significant, there were trends toward the AN group having lower total and low-density lipoprotein (LDL) cholesterol and higher...
alanine aminotransferase (ALT). The AN group had significantly higher CRP compared with the non-AN group. HbA1c levels were higher in the AN, compared with the non-AN, group. There was no difference between groups for fasting glucose level; however, fasting insulin was significantly higher in the AN group.

Figure 1 displays the glucose and insulin dynamics during the OGTT in the AN and non-AN groups. Overall glucose response during OGTT was higher in the AN group with a significant difference at the 60-minute time point (AN = 134.9 ± 35.3 mg/dL vs non-AN = 123.6 ± 30.4 mg/dL, P = .04). Similarly, insulin response during the OGTT was higher in the AN group with significant differences at the 30-minute (AN = 162.5 ± 86.4 mU/L vs non-AN = 123.4 ± 67.9 mU/L, P = .003), 60-minute (AN = 161.8 ± 85.6 mU/L vs non-AN = 119.6 ± 79.9 mU/L, P = .003), and 90-minute (AN = 160.9 ± 98.0 mU/L vs non-AN = 119.2 ± 97.5 mU/L, P = .012) time points.
Discussion

Results of our study suggest that, independent of BMI, obese children with AN have higher levels of basal and glucose-stimulated insulin compared with obese children without AN. There was also a suggestion of slightly elevated plasma glucose at the 60-minute time point during OGTT. Our findings are in agreement with others\(^2,4\) who have suggested that AN is associated with hyperinsulinemia and impaired glucose metabolism. However, the current results are at odds with other reports demonstrating that AN is not a reliable clinical marker of hyperinsulinemia and insulin resistance when fat mass is taken into account.\(^3,7\) Although the patients with AN in our study had higher BMI than non-AN controls, the differences in insulin levels persisted, despite adjustments for BMI level.

Despite having a clearly increased insulin response during the glucose challenge, children with AN did not demonstrate consistently elevated levels of glucose during the OGTT, with slightly higher levels noted only at the 60-minute time point. These findings suggest that obese children with AN are able to maintain nearly appropriate postprandial glucose levels at the expense of compensatory hyperinsulinemia. Even though fasting glucose levels did not differ significantly between groups, HbA1c, a marker of chronic glycemic control, was higher in patients with AN. Although HbA1c levels were in the normal range, these findings, along with the slightly elevated glucose and greatly exaggerated postprandial hyperinsulinemia, suggest that glucose and insulin metabolism are abnormal in obese children with AN.

Levels of CRP were elevated in the AN group suggesting that systemic inflammation may be higher in this condition. However, these finding should be interpreted with caution because not all CRP tests were performed with a high-sensitivity assay. Therefore, the finding of elevated levels of inflammation in obese children with AN should be considered hypothesis generating and should be explored in future studies.

Some limitations to this study should be noted. Tanner stage data were not available from the medical charts. Although the AN and non-AN groups were well matched for age, without Tanner stage data we were unable to confirm that pubertal status was similar between groups. Race was not documented in the medical charts. This is relevant since different prevalence rates have been reported among different racial groups. In particular, African Americans have higher rates of AN compared with other racial groups.\(^8\)

In conclusion, findings from this study suggest that the presence of AN in obese children is associated with fasting and postprandial hyperinsulinemia. Therefore, AN may be a useful clinical marker to identify obese children at increased risk of developing future type 2 diabetes. The chronic and dynamic state of compensatory hyperinsulinemia in AN may be an early sign of metabolic dysregulation and a potential target of therapy. However, further prospective and controlled studies are needed to confirm these findings and determine whether obese children with AN should undergo more aggressive risk factor screening and management.

Declaration of Conflicting Interests

The authors declare that they do not have any conflict of interest.

References