

HYPERINSULINEMIA AND ACANTHOSIS NIGRICANS IN AFRICAN AMERICANS

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Compared with the US white, non-Hispanic population, the African-American population has a nearly two-fold higher prevalence of noninsulin-dependent diabetes mellitus (NIDDM). Obesity, which usually precedes NIDDM, is associated with the skin lesion acanthosis nigricans in African Americans. This study was undertaken to determine what the relationship of acanthosis nigricans was to hyperinsulinemia, a major risk factor for NIDDM. Eighty-nine African-American subjects with acanthosis nigricans and 25 others without the skin lesion were evaluated using oral glucose tolerance testing and responsiveness to insulin. Noninsulin-dependent diabetes mellitus was present in 19 of the subjects with acanthosis nigricans. The prevalence of NIDDM in this group increased with increasing age, reaching 50% among those in their 40s. Fasting plasma insulin concentration was in direct proportion to the severity of the acanthosis nigricans involvement of the neck. These data suggest that among African Americans, this skin lesion is a marker for hyperinsulinemia and insulin resistance. Furthermore, the presence of acanthosis nigricans identifies a subset with a much higher prevalence of NIDDM than is present in African Americans in the general population. (*J Natl Med Assoc.* 1997;89:523-527.)

Key words: diabetes ♦ obesity ♦ African Americans ♦ acanthosis nigricans ♦ hyperinsulinemia

The NHANES II study, performed between 1976 and 1980, demonstrated diabetes prevalence rates of 9.9% and 6.4% for African Americans and white Americans, respectively.¹ Half of those in both ethnic groups with diabetes were undiagnosed prior to the

glucose tolerance testing performed as part of the study. In each age interval tested, the prevalence of diabetes was higher among African Americans than among whites. In the 55 to 64 age group, the prevalence rates were 22.5% and 12.5%, and in the 65 to 74 age group, the prevalence rates were 26.4% and 17.9% for African Americans and whites, respectively.¹

We previously documented a 13% prevalence of acanthosis nigricans among unselected African-American teenagers in the Galveston public schools.² This prevalence was 25-fold higher than among age, weight, and gender-matched white, non-Hispanic students.² Acanthosis nigricans is seen in patients with insulin resistance and hyperinsulinemia,²⁻⁴ and hyperinsulinemia is a major risk factor for the development of noninsulin-dependent diabetes mellitus (NIDDM).⁵⁻⁷ This article reports that the severity of the skin lesion is related directly to fasting plasma insulin concentrations. Based on

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Table. Patient Characteristics*

| | Acanthosis Nigricans | No Skin Lesion |
|--|----------------------|----------------|
| No. subjects | 89 | 25 |
| Acanthosis nigricans neck grades† | | |
| Grade 0 | — | 25 |
| Grade 1 | 23 | — |
| Grade 2 | 38 | — |
| Grade 3 | 3 | — |
| Grade 4 | 9 | — |
| Gender | | |
| Male | 17 | 16 |
| Female | 72 | 9 |
| Age (years) | 24±2 | 35±2 |
| Weight (% of ideal) | 184±4 | 129±4 |
| Body mass index (kg/m ²) | 34.5±0.8 | 25.2±0.7 |
| Obesity | 87 (98%) | 17 (68%) |
| Noninsulin-dependent diabetes mellitus | 16 (18%) | 3 (12%) |
| Impaired glucose tolerance | 15 (17%) | 0 (0%) |
| Fasting plasma insulin (μU/mL) | | |
| All subjects | 38±2 | 16±2 |
| Noninsulin-dependent diabetes mellitus | 51±8 | 34±8 |
| Impaired glucose tolerance | 51±6 | NA |
| Nondiabetic | 32±2 | 14±2 |
| K _{ITT} (% fall per min) | 2.6±0.2 | 4.4±0.8 |

*N=114.
 †Grades are based on vertical width of the posterior neck lesion: <1 cm=grade 1, 1 to 2 cm=grade 2, 2 to 3 cm=grade 3, and >3 cm=grade 4.

cross-sectional observations, it appears that among African-American subjects with acanthosis nigricans, NIDDM becomes highly prevalent with increasing age.

METHODS

Subject Selection

All subjects in this report identified themselves as African Americans and were selected for study because they had the skin lesion acanthosis nigricans. The point of contact before referral for study was often gynecological endocrinology where the initial complaints were infertility, amenorrhea, or hirsutism (35 subjects). Of the remaining 54 patients, 12 were seen by pediatric endocrinology because of obesity, 5 subjects were referred from the dermatology clinic, and 37 subjects came by referral from internal medicine outpatient clinics. Twenty-five African-American subjects who did not have the skin lesion were recruited to verify the hypothetical relationship of the acanthosis nigricans skin lesion with hyperinsulinemia in this eth-

nic group. The Table displays patients characteristics divided by presence or absence of the skin lesion.

Acanthosis Nigricans Severity

The posterior neck of each subject was examined for the presence of the dark, thickened, and rough skin that is characteristic of acanthosis nigricans. The severity is graded as trace if the lesion clearly is present but does not extend continuously across the back of the neck; grade 1 describes a continuous line across the back of the neck up to one 1 cm in vertical height; grade 2 describes the skin lesion up to 2 cm in height; grade 3 describes the lesion up to 3 cm in height; and grade 4 describes extensive involvement of the neck measuring >3 cm in vertical height. Color plates illustrating the grading scheme have been published previously.²

Glucose Tolerance and Insulin Responsiveness

Oral glucose tolerance testing was performed according to the methods recommended by the

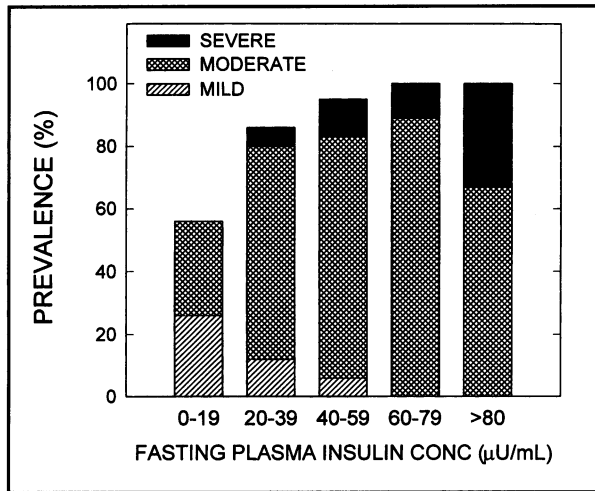


Figure 1. Graph illustrating the severity of acanthosis nigricans on the posterior neck in African Americans. The relationship of fasting plasma insulin concentration to the prevalence of mild, moderate, and severe acanthosis nigricans on the back of the neck is plotted against the fasting plasma insulin concentration range shown on the abscissa.

World Health Organization.⁸ After at least 1 day of a diet containing 300 g of carbohydrates, subjects fasted for 12 hours and were administered 75 g of glucose orally. Blood was drawn at 0 and 120 minutes for glucose and insulin measurements.

Interpretation of the glucose response followed the criteria of the World Health Organization.^{8,9} Fasting and 120-minute samples of <140 mg/dL were considered normal. Fasting value ≥ 140 mg/dL or 120 minute sample ≥ 200 mg/dL defined diabetes. If the fasting glucose determination was normal, but the 120-minute value was 140 to 199, the test result was designated impaired glucose tolerance.⁹

Plasma glucose was measured using a glucose oxidase method, and plasma insulin concentration was quantitated using a double antibody radioimmunoassay.¹⁰ Free insulin concentrations were measured in those patients who previously had received exogenous insulin.¹⁰ Responsiveness to exogenous insulin was measured by administering a bolus of regular human insulin at 0.1 unit/kg and obtaining samples for plasma glucose determinations every 5 minutes for 30 minutes. The rate of fall in glucose between 5 and 20 minutes after the bolus was termed K_{ITT} and reported as percent fall per minute during that period of time.¹¹

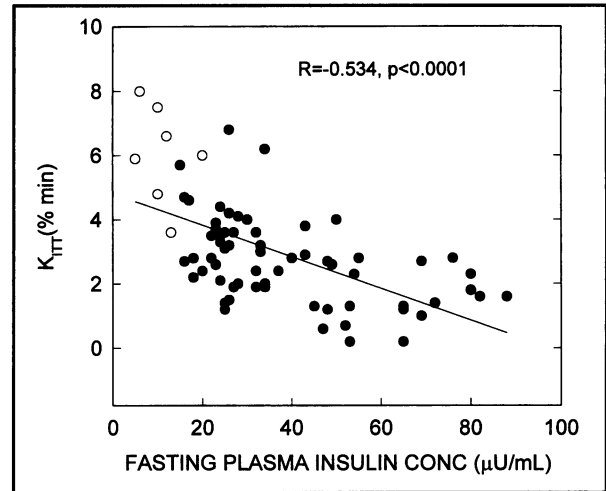


Figure 2. Chart depicting the relationship between fasting plasma insulin and insulin responsiveness. The points displayed represent the fasting plasma insulin concentration versus the K_{ITT} determined during the initial study protocol for 71 African-American subjects, 7 of whom did not have acanthosis nigricans (open circles).

RESULTS

Hyperinsulinemia and Acanthosis Nigricans Severity

Figure 1 displays the prevalence of the graded severity of acanthosis nigricans on the back of the neck of each subject examined. Twenty-five subjects included in this analysis did not have the skin lesion. Subjects graded "trace" or "1" were considered mild; those graded "2" or "3" were considered to have moderate severity; and those graded "4" were considered to be severely affected.

These data showed a correlation of neck acanthosis nigricans severity with fasting plasma insulin ($R=0.496$; $n=114$; $P<.001$). Other regions (axillae, inner thighs, abdominal folds, and other) also were graded for each subject as described previously.⁴ These grades were summed as an acanthosis score for each individual. This acanthosis score also was correlated with fasting plasma insulin concentration ($R=0.477$; $n=114$; $P<.001$), similar to the correlation previously reported for an ethnically mixed group.²

Insulin Responsiveness

Sixty-four subjects with acanthosis nigricans and 7 subjects without the skin lesion underwent a standardized insulin challenge as described in Methods

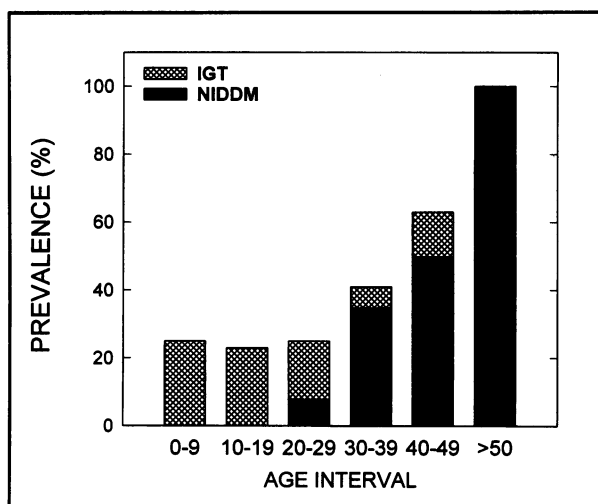


Figure 3.

Graph illustrating glucose tolerance among African Americans with acanthosis nigricans. The prevalence of noninsulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance (IGT) among individuals in the age intervals shown is plotted.

above. Figure 2 shows the K_{ITT} plotted versus the fasting plasma insulin value. Linear regression through these data showed a highly significant negative correlation ($R=-0.534$; $n=71$; $P<.001$).

Glucose Tolerance Testing Among 89 Subjects With Acanthosis Nigricans

Noninsulin-dependent diabetes mellitus had been diagnosed in 14 of the subjects with acanthosis nigricans prior to the study, but NIDDM by oral glucose tolerance testing⁹ was found in 5 additional subjects. Impaired glucose tolerance was found in 15 subjects. The relationship of NIDDM and impaired glucose tolerance to age is shown in Figure 3. The prevalence of NIDDM increased in each decade from age 20 to 50. Five subjects >50 had NIDDM.

DISCUSSION

Acanthosis nigricans is a common skin lesion among African Americans.² The presence of this skin lesion is strongly associated with obesity among African-American adolescents.² The studies described in this report demonstrate that the skin lesion in this ethnic group strongly correlates with hyperinsulinemia and insulin resistance.

Harris et al¹ reported a prevalence of diabetes among African Americans that was nearly twice that of age-matched white Americans. In the subset of

African Americans <50 years old who were identified as having acanthosis nigricans, the age-related prevalence of NIDDM is six-fold higher than Harris¹ found in age-matched African Americans and nearly 10-fold higher than the age-matched white population evaluated in the NHANES II studies.

Diabetes is one of several health problems with excess prevalence among African Americans. In many of these problems, socioeconomic factors confound potential genetic explanations. The prevalence of hypertension in African Americans is twice that of white, non-Hispanic Americans.^{12,13} Hypertension among African Americans is largely responsible for a two-fold higher incidence of stroke and a nearly three-fold higher incidence of end stage renal failure.¹⁴⁻¹⁶ Hypertension is not common in the people currently indigenous to regions of Africa, who share ancestry with African Americans, suggesting that excess hypertension among African Americans is not determined genetically in a simple way.¹⁷

The causes of these differences in the health status between ethnic groups are complex. The simplest reason would be that the groups are genetically different such that susceptibility to various conditions is significantly higher. However, socioeconomic factors may be more important in some cases. Coronary artery disease may be no more prevalent in African-American males than among white males, but the survival rate after an acute myocardial infarction is less.^{15,17,18} Obesity is more prevalent among adult African Americans than the general population, but this excess prevalence is restricted largely to low-income African Americans.¹⁹

Malignancies have an 11% higher incidence overall among African Americans,^{17,20} particularly lung, pancreas, esophagus, laryngeal, cervical, and prostate cancers.²¹⁻²³ Breast cancer has a lower incidence among African Americans, but whites have a better survival rate.^{17,24} Baquet et al²⁵ suggest that the excess cancer burden among African Americans can be entirely accounted for by socioeconomic factors. They suggested that if adjustments were made for socioeconomic status, the lung cancer incidence would actually be lower in African Americans compared with whites. Sawyer et al²⁶ and Hayward et al²⁷ have suggested that cancer mortality is higher among poor African Americans because of barriers to access to health care, poorer quality of care, and lack of continuity of care.

In our evaluation of acanthosis nigricans and dia-

betes prevalence in African Americans, we did not attempt to make adjustments for family income or education. The insulin insensitivity in subjects with acanthosis nigricans has been shown previously to be largely hereditary,²⁸ but socioeconomic status also might contribute additional factors through inadequate preventive health measures.¹⁹

Even though benign acanthosis nigricans is common and the association of acanthosis nigricans with internal malignancy is rare, cancer should be considered in subjects who are >35 years of age, with special attention to individuals who are nonobese.

CONCLUSION

The data presented in this report show a strong correlation between the severity of acanthosis nigricans on the back of the neck of African Americans and insulin resistance as quantitated by KITT and fasting hyperinsulinemia. The presence of this skin lesion in an African American may indicate a nearly 10-fold higher risk for developing NIDDM than that reported for the US white population and a six-fold higher risk than the general population of African Americans.

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