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The Association between Acanthosis Nigricans and Dysglycemia in an Ethnically Diverse Group of Eighth Grade Students

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Abstract

The purpose of this study was to describe the prevalence of acanthosis nigricans (AN) and to quantify its association with dysglycemia in an ethnically diverse group of eighth grade students. Data were collected in 2003 from a cross-sectional study of students from 12 middle schools in three U.S. states. Sex, race/ethnicity and pubertal status were self-reported. Anthropometric measures were recorded. Trained staff identified the presence and severity of AN by inspection of the back of the neck. Fasting and 2hr blood samples were analyzed for impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and high-risk glycated hemoglobin (A1C), respectively defined as ≥100 mg/dl, ≥140 mg/dl, and ≥ 5.7-6.4%. Overall, 25.0%, 58.2%, and 16.8% were Black, Hispanic and White, respectively. AN was present among 406 /1438 (28.2%) of students: 39% among Black, 30% among Hispanic, and 5.4% among White. IGT and highArisk A1C were present among 2.1%, and 12.4%, respectively. In multivariate logistic modeling after adjusting for gender, family history of diabetes, BMI percentile and pubertal staging, the presence (vs. absence) of AN was associated with a 59% increased likelihood of highArisk A1C: (P = 0.04), twice the likelihood of IGT (P=0.06), and 47% greater likelihood of IGT/IFG combined (P<0.0001). Adjustment for insulin attenuated the ORs by 25-70%. In a racially/ethnically diverse sample of U.S. adolescents, AN was common, occurring in 28% of the sample. AN was associated with a

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HEALTHY intervention materials are available for download at http://www.healthystudy.org/.

DISCLOSURE None

50-100% increased likelihood of dysglycemia even after consideration of established diabetes risk factors.

Keywords

acanthosis nigricans; glycosilated hemoglobin; hyperglycemia; insulin resistance; screening; adolescents

INTRODUCTION

Type 2 diabetes is an international public health problem (1). Once considered exclusively an adult chronic disease it has been diagnosed more frequently in the United States among children and adolescents. It now comprises an increasingly large proportion (8-45%) of newly diagnosed diabetes cases (2, 3), especially among minority youth 10 to 19 years of age (4). Moreover, precursor states to type 2 diabetes including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have become more prevalent among adolescents (5-7).

Acanthosis nigricans (AN) is a disorder of the skin characterized by hyperpigmentation, hyperkeratosis, and papillomatosis, presenting as darkish blackish- brown, velvety lesions most often on the back of the neck, but also on other areas of the body, especially those that are prone to perspiration or friction (8). AN has been associated with rare, genetic defects in insulin action, i.e., Type A insulin resistance and internal malignant neoplasms, especially adenocarcinomas. (8, 9). The increase in circulating insulin levels manifested in hyperinsulinemia results in the binding and stimulation of insulin receptors and growth factor-1 receptors on keratinocytes and dermal fibroblasts (10). Thus, AN is a visible, clinical marker of hyperinsulinemia.

AN is more prevalent among persons of minority race than whites (11, 12). In addition, strong associations have been demonstrated between AN and excess body weight (13, 14), hyperinsulinemia, homeostasis model assessment insulin resistance (HOMA-IR), and directly measured insulin sensitivity (S_i) (11, 13-16). But, the use of varying indexes, as well as the lack of a standardized assay and a universally accepted threshold of insulin resistance, hampers both the ability to quantify the association between AN and insulin resistance, and to compare study results (17). Laboratory analyses of glucose concentrations, in contrast, are standardized and clinical cut points well-established, thereby enabling comparisons of risk estimates between studies.

Clinical studies that have reported on the association between glucose concentrations and AN have been restricted to mostly or exclusively overweight or obese children. For example, among 160 obese Turkish children (mean age 10.4 ± 3.3 years) followed at a pediatric endocrinology clinic, no significant differences in mean fasting or 2 hr postAload glucose concentrations were noted between children with and without AN (14). Similarly, no differences were noted among 139 overweight African American and White 6 to 10 year olds (18). In contrast, among 287 obese children 8-14 years from urban primary pediatric offices, children with AN had a higher prevalence of abnormal glucose homeostasis than

children without AN (19). Although several school-based studies have described the prevalence of AN (12, 20) and its association with insulin sensitivity (11), only one has specifically examined AN and impaired glucose metabolism (21).

The aim of this study was to examine the prevalence of AN, and to quantify its association with aspects of impaired glucose homeostasis among a racially/ethnically diverse sample of eighth grade students from lower income schools.

RESEARCH DESIGN AND METHODS

The data presented here are from a pilot study conducted by the Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) Prevention Study Group. STOPP-T2D Prevention is a National Institute of Diabetes and Digestive and Kidney Diseases sponsored multisite study designed to reduce the prevalence of risk factors for type 2 diabetes among middle school children. Data were collected at three field centers in Texas (Baylor College of Medicine), California (University of California, Irvine), and North Carolina (University of North Carolina at Chapel Hill). The STOPP-T2D coordinating center was at The George Washington University Biostatistics Center (Rockville, MD). The institutional review boards at each site approved this study.

Participant recruitment methods and inclusion criteria have been reported elsewhere (22). In brief, participants were eighth grade students recruited from 12 schools (4 per field center), in which at least 50% of the participants were from a minority race/ethnicity. Schools were also required to have at least 50% of their enrolled students eligible for free or reduced price school lunch. All eighth grade students who provided written parental consent and childhood assent and who did not have a diagnosis of either type 1 or type 2 diabetes were eligible to participate. Participants received 50 US dollars and a free breakfast for participating in the study.

Participant ethnicity (Hispanic yes/no) and race were asked of each student as two separate questions with laminated cards showing and defining choices. To assess the presence of AN, staff trained by experienced physicians inspected the most commonly affected area (23, 24), the back of the neck. AN may be present on other areas of the body, but in light of the school setting, large sample size and student participants, the back of the neck was the only site selected for evaluation given its obvious ease of examination which does not require disrobing. Severity was recorded using Burke's scale (23): 0 = Absent: not detectable on close inspection; 1 = Present: clearly present on close visual inspection, not visible to the, casual observer, extent not measurable; 2 = Mild: limited to the base of the skull, does not extend to the lateral margins of the neck (usually < 3″ or 8 cm in breadth); 3 = Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid; usually 3-6″ or 8-16 cm), should not be visible when the participant is viewed from the front; 4 = Severe: extending anteriorly (> 6″ or 16 cm), visible when the participant is viewed from the front. AN was considered absent if the score was <1 and present if the scale score was ≥1. Pubertal development was selfAassessed using the Pubertal Development Scale (25). Height was measured to the nearest 0.1 cm on a stadiometer (PEAAIMA101; Perspective Enterprises, Kalamazoo, MI) with the participants shoeless and the head in the

Frankfort plane. Body weight was measured to the nearest 0.1 kg using a calibrated electronic scale (SECA Alpha 882; Vogel & Halke, Hamburg, Germany) with the participants shoeless and pockets empty. BMI (weight in kilograms divided by the square of height in meters) and BMI percentiles were then calculated using Centers for Disease Control and Prevention ageA and sexAspecific percentiles; participants were grouped as normal weight (BMI <85th percentile), overweight (BMI 85th -94th percentile), obese (BMI ≥95thA98th percentile) and severely obese (BMI ≥ 99th percentile). Waist circumference was assessed to the nearest 0.1 cm at the lateral border of the right iliac crest according to the NHANES protocol with use of a weighted measuring tape by research assistants who were within 90% agreement with a criterion observer during a preAstudy training procedure. Participants were called the night before the blood sampling and reminded that they needed to fast before the test. At the beginning of the blood sampling, participants were asked when they last ate; any participant who reported eating or drinking after midnight was considered nonfasting and asked to return another time when still eligible for the incentive. No participants reported taking any lipid-lowering or antihypertensive medications. Fasting venous blood samples were obtained by experienced phlebotomists to determine insulin, glucose and HbA_{1c}% (A1C). Blood was collected in 2-ml Vacutainers (Becton Dickinson, Franklin Lakes, NJ) containing sodium fluoride for glucose and sodium heparin for insulin. Students were then given oral glucose (solution 1.75 g/kg to a maximal dose of 75g).Two hours post-glucose load, another blood sample was obtained to determine glucose levels. Glucose was assessed using a Hitachi 917 autoanalyzer by the Hexokinase method using reagent from Roche Diagnostics. The measurement of relative proportion of hemoglobin subclasses and calculation of the HbA1c level was performed using an automated non-porous ion exchange high performance liquid chromatography system (G-7 Tosoh Biosciences, Inc.). The intra-assay CV is 0.047% and the inter-assay CV 0.070%. IFG and IGT were defined according to the American Diabetes Association's (ADA) criteria (26). A1C cutpoints of <5.7% and 5.7-6.4% were classified as normal and high-risk, respectively (27). Students with type 2 diabetes identified by FPG ≥125 mg/dl or OGTT ≥200mg/dl or A1C >6.4% were not eligible for inclusion in this report (n=12). Blood was spun and separated into serum and plasma, frozen, packed in dry ice, and shipped to the Northwest Lipid Metabolism and Diabetes Research Laboratory at the University of Washington.

Statistical Analysis

Descriptive statistics including means, SDs, and percentages were calculated for all variables. Generalized estimating equation (GEE) models that took into account the clustering of observations within schools were used to test for differences in demographics, metabolic profile and clinical measures between those with and without AN. Equal correlation between all interschool observations (exchangeable) was chosen as the covariance structure. Three logistic regression GEE models were used to predict IGT, IFG and/or IGT combined, and highArisk A1C by AN presence vs. absence. Model 1 adjusts for gender, family history of diabetes, and racial/ethnic group. In order to assess possible confounding, BMI percentile and pubertal stage were added to the variables in the first model to create Model 2. An additional adjustment for fasting insulin (log transformed) was added in Model 3 which included all the variables in models 1 and 2) A multivariate approach was used to examine possible interactions among gender and race/ethnicity and

BMI with AN. Because none of the interactions were significant, they were removed from all models. All descriptive data from this pilot study of a multisite trial are considered exploratory and thus all *P* values are presented without adjustment for multiple comparisons with α set at 0.05. SAS statistical software (version 9.2; SAS Institute, Cary NC) was used for all statistical analyses.

RESULTS

A total of 1,740 eighth grade students participated in the study. Twelve students were excluded due to having type 2 diabetes. However, complete data was not collected on all students. One hundred forty-five students were excluded for incomplete data. American-Indians (AI) n= 43 and other race (n=102) were excluded leaving 1,438 participants for these analyses. No significant differences were noted in metabolic, clinical or demographic characteristics between youth included in the analysis (n=1438) and those excluded (n=302). Table 1 shows the results for the overall sample and by AN presence and absence. The racial distribution was 25% Black, 58.2% Hispanic, and 16.8 % White; mean age was 13.6 (0.6) years and 56.9% were female. Overall, 406 of 1438 (28.2%) students had AN; 39%, 30%, and 5.4% among, Black, Hispanic and White, respectively (data not shown). The prevalence of a family history of diabetes was 12% overall, significantly higher among those with AN present vs. absent (17% vs. 10%, P < 0.0004). Overall,12.4% had high-risk A1C, 2.1% had IGT and 40.3% had IFG. The number of students with IFG/IGT was n=584: 165 (28%) of whom had AN present. Nearly 50% of students had a BMI ≥ 85th percentile: 22.3% were obese and 6.3% of students were severely obese, BMI ≥ 99th percentile

Students with AN showed a less favorable metabolic profile compared to students without AN (Table 1). For example, 10.1% of students without AN and 18. 2% with AN had highArisk A1C. IGT was twice as high in the AN present vs. AN negative group (3.8% vs. 1.5%, *P* < 0.0005). Among students with AN the prevalence of BMI ≥ 95th percentile was nearly four times higher than that among students without AN (60.4% vs. 16.1%). A greater proportion of students with AN were at a Tanner staging of 4 or 5 (*P* < 0.0001).

To quantify the association between AN with IGT, IFG/IGT combined, and high-risk A1C, logistic regression models were used to estimate the OR (95% CI) after adjustments for covariates. Compared to students without AN, among students with AN, the OR of IGT (vs. NGT) was 2.30 (95% CI 1.24- 4.23) after adjustment for race/ethnicity, gender, and family history of diabetes. Additional adjustment for BMI percentile and Tanner staging (Model 2) attenuated the association (OR 2.02, P =0.06. Inclusion of fasting insulin in the model attenuated the association by 70%. (Table 2)

Table 2 shows the multivariate association between AN and high-risk A1C. Compared to students without AN, among persons with AN, the OR of high-risk A1C was 1.71 (95% CI: 1.07-2.75), which remained essentially unchanged after adjustment for the addition of Model 2 covariates. Again, when insulin was added to the modeling, the association was attenuated but no longer significant. When IGT/ IFG were combined, the OR among those with AN was 1.47(P < 0.0001). Further adjustment for insulin attenuated the OR to 1.22 (p

=0.05). In an analysis that was restricted to Blacks and Hispanics only, the results were essentially the same (data not shown).

Figure 1 shows the mean BMI (standard error) percentile by AN severity only among Blacks and Hispanics; whites were excluded because of their low prevalence of AN. For Blacks and Hispanics AN is absent at BMI < 70th percentile. The slight presence of AN appears among Blacks at a lower mean BMI percentile than it does among Hispanics, 76th and 86th percentile respectively. Mild AN is also evident at a lower BMI percentile among Blacks than Hispanics, 85th and 95th percentile respectively. In contrast, moderate and severe AN are noted at BMI 95th percentile for both race groups. No significant difference was noted in mean BMI percentile between Blacks and Hispanics overall (74.1 vs. 76.6, respectively); moreover, Blacks were significantly more likely to have highArisk A1C (15.1% vs. 10.7%) (data not shown). Among normal weight Blacks with and without AN the only significant differences were noted between mean 2hr insulin (88.5 vs. 75.0 μU/dL, P<0.0001) and FPG (93.0 vs. 97.0 mg/dL, P= 0.007) (data not shown). These differences were not noted among normal weight Hispanic students.

CONCLUSION

In this racially/ethnically diverse sample of eighth grade adolescents the overall prevalence of AN was 28.2% and varied by race: 39%, 30%, and 5.4% among, Blacks, Hispanics and Whites, respectively. These results are remarkably similar to another school-based screening program of 854 obese youth (mean age 11.4 years, 75% Black, at least 50% eligible for free/ reduced lunch) (21). In that study, the prevalence of AN was 26%: 31%, 10.7% and 6.7% among Black, Hispanic and White students respectively. In contrast, the prevalence estimates in the present study are somewhat higher than in other studies. For example, in a convenience sample of 6th through 8th grade students (n=675) in New Mexico, (mean age 13.5 years, 19% Native-American and 46.5% Hispanic, 26.6% obese) 19.7% of Hispanics, 38.6% of Native-Americans, and 5.4% Whites had AN (11). In another school -based screening of 1,412 students in 6th and 8th grade (mean age 13.4 years, 27% obese) in Texas, the prevalence of AN was 7.1% overall; 13%, 5.5% and 0.4% among Blacks, Hispanics and Whites, respectively. (12) Finally, among 102,733 youth in 3rd, 5th and 8th grades (8 -15 years) in Dallas (20), the overall prevalence of AN was 14.4%. One reason for the higher prevalence observed in the present study is the higher proportion (50%) of overweight/ obesity among these students, which in part reflects the secular trend toward increased obesity. Further, a higher proportion of our subjects were pubertal, with nearly 85% in Tanner Stages 3 and 4 (which corresponds to the period of greatest insulin resistance) (28). Finally, the proportion of Black and Hispanic students in this study was nearly 85%.

This study expands the literature by quantifying the risk between AN and several dysglycemic states that are in the pathophysiolgic pathway of the natural history of type 2 diabetes. AN was associated with a two-fold increased likelihood of IGT, a 60% increased likelihood of high-risk A1C, and a 50% increased likelihood of IFG/IGT combined, even after adjustment for pubertal development and BMI percentile, suggesting that AN confers an additional risk of dysglycemia beyond obesity, consistent with some reports (11, 29). AN was not associated with IFG, i.e. elevated fasting plasma glucose (FPG), alone in any

multivariate modeling (data not shown), possibly due to the high prevalence (40%) among persons with and without AN; the lack of variability between groups may mask an association, if there is one. Further explanation for this lack of association comes from the fact that mechanisms which control plasma glucose concentration during the fasting state are different from those that regulate plasma glucose after a meal (27). FPG is primarily determined by the rate of hepatic glucose production, which relates to hepatic, rather than peripheral, insulin resistance (30). On the other hand, postAprandial glucose concentrations are determined by the rate of glucose stimulated insulin secretion and skeletal muscle insulin sensitivity. As these two entities (hepatic and peripheral insulin resistance) are intertwined, it seems logical to associate fasting plasma glucose (and IFG) with peripheral insulin resistance. However, discordance between these measurements of glycemic control is often encountered (31). Moreover, IFG is also correlated with reduced beta cell function among nondiabetic children and this may provide another epidemiologic avenue for the association with AN (32). The attenuation of the odds ratios after adding insulin in the modeling underscores the strong influence it has on dysglycemia; that is, when insulin is taken into account the association between AN and dysglycemia reflects the association of insulin resistance with dysglycemia.

Previous studies, have focused on the association between AN and elevated levels of insulin, or insulin resistance. The difficulty with insulin assessments is the lack of a standardized insulin assay or a universal threshold to classify persons with and without insulin resistance. As a consequence, comparing risk between studies has been hampered (17). In contrast, quantifying risk estimates based on clinically established cutpoints of glucose measurements has the advantage of allowing meaningful comparisons between studies; moreover, the results are easily interpretable.

Furthermore, AN was present among Blacks even in the absence of elevated BMI. Similar findings have been reported in other race groups (13, 29, 33, 34). The ADA recommends screening for type 2 diabetes among asymptomatic children with a BMI >85th percentile for age and sex, plus two additional risk factors. Our findings suggest that non-obese Black youth may be overlooked for screening, and the opportunity for targeted intervention to prevent or delay the onset of diabetes may be missed. Based on our data, the only metabolic difference between normal weight youth with and without AN was the 2hr insulin concentration, corroborating other studies that have reported African American youth have higher concentrations of insulin than white youth (35-37).

One of the major strengths of this study was the collection and assessment of covariates that had not been available in other school -based samples, namely pubertal staging, the OGTT and A1C. In multivariate analyses we were able to take into account the effects of pubertal development, a period of transitory insulin resistance (38, 39) on the dysglycemic states. Also, the narrow age range in the sample reduced the confounding effect of age -related changes in insulin sensitivity on glycemia.

Some limitations are worthy of mention. With regard to the assessment of AN, we were unable to evaluate the between or within rater variability of AN. However, Burke et al.(23) reported >80% inter-observer agreement when identifying AN on the back of the neck and

Nguyen et al. (18) reported 100% concordance between raters for the presence or absence of AN. Furthermore, over 90% of the time AN will be apparent on the neck (12, 23, 24). Another limitation is the cross-sectional design, impeding the ability to establish temporal associations and causation.

In summary, AN is associated with an approximately 50% increased likelihood of several dysglycemic states known to herald the development of type 2 diabetes. Although AN will not be present in every high-risk youth, it is an easily identifiable clinical marker of IGT and high-risk A1C.

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List of Abbreviations and Acronyms

(AN)	Acanthosis nigricans
(BMI)	Body mass index
(CI)	Confidence interval
(IFG)	Impaired fasting glucose
(IGT)	Impaired glucose tolerance
(A1C)	Glycated hemoglobin A1C
(HOMAAIR)	Homeostasis model assessment –insulin resistance
(OGTT)	Oral glucose tolerance test
(OR)	Odds Ratio

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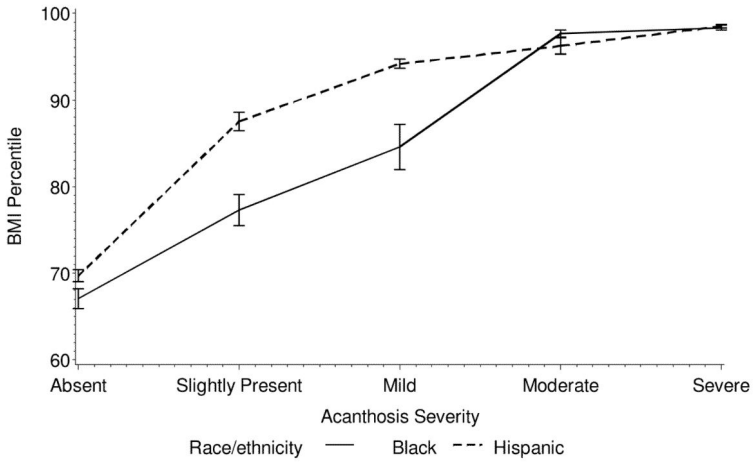

Figure 1.

Mean (SE) BMI Percentile by AN Severity by Race/Ethnicity.

Footnotes: 0 = Absent: not detectable on close inspection; 1 = Slightly Present: clearly present on close visual inspection, not visible to the, casual observer, extent not measurable; 2 = Mild: limited to the base of the skull, does not extend to the lateral margins of the neck (usually < 3″ or 8 cm in breadth); 3 = Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid; usually 3-6″ or 8-16 cm), should not be visible when the participant is viewed from the front; 4 = Severe: extending anteriorly (> 6″ or 16 cm), visible when the participant is viewed from the front.

Table 1

demographics, metabolic and clinical profile of cohort and by AN status

		Acanthosis Nigricans		
	Overall (n=1438) Mean (SD) or %	***Present (N=406) Mean (SD) or %***	***Absent (N=1032) Mean (SD) or %***	***P-value***
DEMOGRAPHIC DATA				
Race/Ethnic Group				
Black	25.0%	34.5%	21.3%	<.0001
Hispanic	58.2%	62.3%	56.6%	
White	16.8%	3.2%	22.1%	
Age (yrs)	13.57 (0.62)	13.61 (0.61)	13.55 (0.62)	0.0657
Family History (DM)	11.9%	17.0%	9.9%	0.0004
Female	56.9%	65.5%	53.5%	0.0088
METABOLIC PROFILE				
HbA1c (%) [b]	5.42 (0.30)	5.49 (0.29)	5.39 (0.30)	<.0001
≥ 5.7	12.4%	18.2%	10.1%	0.0263
Fasting Glucose (mg/dL)	97.9 (7.2)	98.0 (7.6)	97.9 (7.1)	0.5244
≥ 100	40.3%	40.1%	40.3%	0.8263
Fasting Insulin μU/mL) [b]	30.2 (19.1)	41.1 (25.0	25.9 (14.1)	<.0001[a]
< 15	12.9%	6.0%	15.6%	<.0001
15 – 29	50.8%	33.3%	57.6%	
≥ 30	36.3%	60.7%	26.8%	
2-Hour Glucose (mg/dL) [b]	97.1 (19.8)	103.4 (19.9)	95.0 (19.3)	<.0001
≥ 140	2.1%	3.8%	1.5%	0.0005
2-Hour Insulin (μU/mL) [b]	101.8 (104.8)	152.8 (145.9)	85.4 (81.2)	<.0001[a]
CLINICAL MEASURES				
Tricep Skinfold (mm)	18.4 (8.5)	24.6 (9.0)	16.0 (6.9)	<.0001[a]
Subscapular Skinfold (mm) [b]	16.5 (9.1)	23.8 (9.9)	13.6 (6.9)	<.0001[a]
BMI (kg/m^2)	24.2 (5.7)	28.9 (6.3)	22.4 (4.3)	<.0001
< 85th pct.	50.5%	18.7%	63.0%	<.0001
85th – 94th pct.	20.9%	20.9%	20.9%	
95th – 98th pct.	22.3%	41.9%	14.5%	
≥ 90th pct.	6.3%	18.5%	1.6%	
Waist Circumference (cm)	80.4 (14.0)	91.4 (15.6)	76.1 (10.6)	<.0001
≥ 90th pct.	21.9%	49.8%	10.9%	<.0001
Tanner Stage				
Stage 1 or 2	8.5%	9.7%	8.0%	<.0001
Stage 3	25.6%	19.2%	28.2%	
Stage 4	59.2%	60.8%	58.5%	
Stage 5	6.7%	10.3%	5.4%	

Table 2

Multivariate Adjusted Odds Ratios (95% CI) of each dysglycemic state comparing AN presence vs. absence in three models.

Model	Dysglycemic State OR (95% CI)		
	IGT	High-risk A1c	IGT/IFG
Model 1	2.29 (1.24, 4.23)**	1.71 (1.07, 2.75)*	1.43 (1.20, 1.70)***
Model 2	2.02 (0.96, 4.22)	1.59 (1.01, 2.49)*	1.47 (1.21, 1.78)***
Model3	1.31 (0.55, 3.10)	1.32 (0.85, 2.06)	1.22 (1.00, 1.49)

Model 1: adjusted for gender, family history and race/ethnicity

Model 2: adjusted Model 1 factors plus BMI percentile and Tanner Staging

Model 3: adjusted for Models 1 and 2 factors plus log transformed fasting insulin (continuous)

* P <0.05

** P < 0.01

*** p <0.001