Sex Hormone-Binding Globulin, Oligomenorrhea, Polycystic Ovary Syndrome, and Childhood Insulin at Age 14 Years Predict Metabolic Syndrome and Class III Obesity at Age 24 Years

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Objective We hypothesized that oligomenorrhea (menstrual cyclicity ≥42 days), hyperandrogenism, low levels of sex hormone-binding globulin (SHBG), childhood insulin, and metabolic syndrome (MetS) at age 14 years would predict MetS and class III obesity (body mass index ≥40 kg/m^2) at age 24 years.

Study design In this prospective study of schoolgirls, at age 14 years, the girls were categorized as regularly cycling (n = 375), oligomenorrheic (n = 18), or oligomenorrhea plus biochemical hyperandrogenism (polycystic ovary syndrome [PCOS]; n = 12), together designated PCOS.

Results Significant explanatory variables for MetS at age 24 years included childhood insulin, MetS, and PCOS category (all positive) and SHBG (negative) at age 14 years. Using categorical data, top decile of childhood insulin, MetS at age 14, bottom decile of SHBG, and PCOS category were significant positive predictors for MetS at age 24. SHBG (negative), black race (positive), and oligomenorrhea (positive) were significant explanatory variables for class III obesity at age 24. Using categorical data, black race, MetS at age 14, bottom decile of SHBG, PCOS category, and top decile of childhood insulin were positive explanatory variables for class III obesity at age 24 years.

Conclusions Oligomenorrhea, PCOS (a subcohort of oligomenorrhea), hyperandrogenism, low SHBG, MetS, and childhood insulin at age 14 years may represent a critical, reversible pathway for the development of MetS and class III obesity in young adulthood. *(J Pediatr 2011;159:308-13)*.

Adolescent oligomenorrhea should point the pediatrician to investigate androgen/estrogen balance and possible underlying polycystic ovary syndrome (PCOS)[1,2] as steps in a critical pathway for development of progressive obesity, the metabolic syndrome (MetS), and early-onset type 2 diabetes mellitus. In adolescents, a low level of sex hormone-binding globulin (SHBG) has been reported to be the only significant predictor of MetS.[3]

Most girls (98% of whites, 97% of blacks) are menarchal at age 14 years.[4] Chiazze et al[5] reported that only 2.5% of 15- to 19-year-old girls had an average menstrual cycle length of >40 days.[5] The National Heart, Lung, and Blood Institute's National Growth and Health Study (NGHS), a 10-year study of black and white girls from age 9-10 to age 18-19,[6] found that >90% of girls had achieved menarche by age 14 years. Defining oligomenorrhea in 15-year-old white Dutch girls as a cycle of ≥42 days, van Hooff et al[1,2] reported that oligomenorrheic girls were more likely than either girls with irregular or normal menses to be hyperandrogenemic and to have polycystic ovaries.

In the current prospective study of black and white girls in the Cincinnati Clinic of the NGHS, we assessed mean pubertal, menstrual, insulin, sex hormone, and MetS data at age 14 years as predictors of MetS and severe (class III) obesity (body mass index [BMI] ≥40) at a mean age of 24 years. We speculated that there are significant roles for oligomenorrhea, PCOS as a subcohort of oligomenorrhea, sex hormones, and insulin at age 14 in the genesis of MetS and class III obesity at age 24, facilitating a pediatric approach to primary prevention of MetS, severe obesity, type 2 diabetes, and adult cardiovascular disease.[7,8]

Methods

The NGHS, initiated in 1987, investigated development of obesity in black and white girls during adolescence.[9] Participant eligibility was limited to girls and their parents who declared themselves as being either black or white and who lived in racially

AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
DHEAS	Dehydroepiandrosterone sulfate
E2	Estradiol
HDL	High-density lipoprotein
MetS	Metabolic syndrome
NGHS	National Growth and Health Study
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone-binding globulin

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Supported in part by National Institutes of Health Grants HL55025, 48941, HL52911, and HL66430 (J.M. and S.D.) and the Lipoprotein Research Fund of the Jewish Hospital of Cincinnati (C.G.). The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.01.018

concordant households. Annual visits were carried out from age 9-10 through age 18-19. The follow-up rate was 89% at the 10th annual visit. Subsequently, investigator-initiated studies were conducted for 5 more years, through age 24-25. In Cincinnati, fasting insulin level was measured at entry, at age 10, and at age 16, and sex steroid hormones and SHBG, along with lipid profiles, apolipoprotein A1, and systolic and diastolic blood pressure, were measured at ages 10, 12, and 14.[10] Sexual maturation was assessed by trained registered nurses.

At each annual visit between age 10 and age 19, information was obtained on menarche and on the number of days since the previous menstrual cycle. Oligomenorrhea at age 14 and age 14-19 was defined as menstrual cycling of ≥42 days.[1,2,5] Separately, we also used 6-year (annual visits between age 14 and age 19) oligomenorrhea categories of 0 (no oligomenorrhea in 6 yearly reports), 1 (1 of 6 reports), 2 (2 of 6 reports), and ≥3 (3 or more of 6 reports) as explanatory variables. We prospectively assessed the relationship between oligomenorrhea and sex hormones at age 14 and MetS and class III obesity at age 24.

Signed informed consent was obtained from each girl's parent or guardian, assent was obtained from each girl in the NGHS, and signed consent was obtained from each girl (now an adult woman) in the extension study.[10]

Laboratory and Clinical Measurements

The methods used to measure SHBG, estradiol (E2), dehydroepiandrosterone sulfate (DHEAS), free testosterone, lipids, apolipoprotein A1, insulin, height, weight, waist circumference, and systolic and diastolic blood pressure have been described previously.[9] Blood was drawn after an overnight fast with the patient seated. Blood draws were not scheduled based on menstrual status or day of menstrual period. BMI was measured annually to assess overweight and waist circumference as an indicator of fat patterning.

At age 14, hyperandrogenism was defined by DHEAS >280 μg/dL, or race-specific bottom decile of SHBG (≤6 nmol/L for black, ≤7 nmol/L for white), or race-specific top decile free testosterone (≥2.13 pg/mL for black and white). At age 14, girls were categorized as regularly cycling, oligomenorrheic, or oligomenorrheic with hyperandrogenism (PCOS, by consensus criteria).[11] These 3 levels were designated PCOS categories.

Girls with a fasting blood glucose level ≥126 mg/dL[12] at age 10 and/or type 1 diabetes (based on patient-physician records) at any time from age 10 through age 25 (n = 7) were excluded from the analysis. Diagnosis of type 1 diabetes was based on fasting glucose ≥126 mg/dL, and self-reported diabetes with treatment by a physician.[12]

At age 10 years and age 16 years, serum insulin was measured after an overnight fast (≥8 hours) by competitive protein-binding radioimmunoassay at the Michigan Diabetes Research and Training Center in Ann Arbor. We designated the first insulin measurement from age 10 (n = 296) and age 16 (n = 95) as "childhood insulin." We used fasting insulin as the indicator of insulin resistance based on a report of Huang et al.[13]

MetS at Age 14 Years and Age 24 Years

We defined MetS at age 14 years using previously reported pediatric standards,[14] with 3 or more of the following 5 components present: triglycerides >110 mg/dL, BMI ≥ age-specific 90th percentile (based on Centers for Disease Control and Prevention 2000 growth charts), blood pressure ≥ age- and height-specific 90th percentile, high-density lipoprotein (HDL) cholesterol ≤50 mg/dL, but with glucose ≥100 mg/dL rather than 110 mg/dL. At age 24, MetS was diagnosed based on revised Adult Treatment Panel III criteria,[15] with 3 or more of the following: waist circumference >88 cm, HDL cholesterol <50 mg/dL, triglycerides ≥150 mg/dL, glucose ≥100 mg/dL, and systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg.

Statistical Analysis

Age 14 risk factors for MetS at age 24 are summarized by race and MetS status in **Table I** (available at www.jpeds.com). Risk factors were categorized as race-specific top or bottom deciles versus the other 9 deciles. Associations between MetS at age 24 and these categorized risk factors were evaluated using the Fisher exact test. Similar evaluations for class III obesity at age 24 are reported in **Table II** (available at www.jpeds.com). The Hochberg-Benjamini correction for multiple tests[16] was used.

Wilcoxon nonparametric tests of difference were used to compare sex hormones (free testosterone, E2, DHEAS, and SHBG) and BMI at age 14 in girls with and without oligomenorrhea at age 14. Stepwise logistic regression analysis was used to assess childhood insulin, age 14 sex hormones, along with race, age, BMI, and waist circumference as explanatory variables for oligomenorrhea (menstrual cycle ≥42 days) at age 14.

To assess age 14 correlates for MetS at age 24, stepwise logistic regression was run. Explanatory variables included race, age 14 measures (oligomenorrhea, PCOS category, MetS status, free testosterone, E2, DHEAS, and SHBG), and childhood insulin (**Table III**). A second logistic regression model was run with the dependent variable 24 MetS at age 24 using race, oligomenorrhea, PCOS category, and MetS at age 14, deciles of age 14 variables (SHBG and E2 [race-specific bottom decile vs top 9 deciles] and free testosterone and DHEAS [race-specific top decile vs lower 9 deciles]), and childhood insulin [race-specific top decile vs lower 9 deciles) (**Table III**). Separately, categorical summation of the number of oligomenorrhea reports at 6 annual visits from age 14-19 (0/6, 1/6, 2/6, or ≥3/6) replaced oligomenorrhea at age 14 (0, 1), and the stepwise logistic regressions were repeated (data not shown).

Age 14 correlates for class III obesity at age 24 were assessed by stepwise logistic regression with the explanatory variables race, age 14 measurements (oligomenorrhea, PCOS category, MetS status, free testosterone, E2, DHEAS, and SHBG), and childhood insulin (**Table IV**). A second logistic regression