Differences between Metabolically Healthy vs Unhealthy Obese Children and Adolescents

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Abstract: Obesity is on the rise worldwide. An obesity subtype, metabolically healthy obese (MHO), is resilient to unfavorable metabolic and cardiovascular effects. Factors predicting MHO phenotype are not well characterized. We aimed to identify MHO and metabolically unhealthy obese (MUO) children and adolescents with respect to metabolic factors, and to find predictors of MHO subtype. A retrospective chart review was done on children, ages 4–19 years, 99% African–American/Caribbean, with BMI ≥95th %tile. MUO was defined as meeting ≥1 of the following: fasting glucose ≥100 mg/dl, HbA1c >5.6%, BP ≥90th %tile, TG ≥150 mg/dl, or HDL <40 mg/dl. Study included 189 subjects, 37.6% were MHO and 62.4% MUO. MHO subjects were younger (mean ± SD, 11.6 ± 3.3 vs 12.9 ± 3.2 years; $p < 0.009$) and had lower BMI %tile (98.4 ± 1.4 vs 98.8 ± 2.1; $p < 0.04$), smaller waist (94.2 ± 15.2 vs 101.4 ± 17 cm; $p < 0.003$) and hip circumferences (105.3 ± 15.6 vs 113.5 ± 15.4 cm; $p < 0.001$), lower fasting insulin (18.5 ± 10.2 vs 24.2 ± 14.3 μU/ml; $p < 0.022$), and lower HOMA-IR (4.1 ± 2.4 vs 5.5 ± 3.6; $p < 0.022$). Acanthosis nigricans was noted less frequently in MHO than MUO ($p < 0.005$). In stepwise logistic regression, age and BMI %tile were significant predictors of MHO. We found that 38% of obese children are MHO. They are younger and have lower BMI %tiles. Lifestyle modification initiated at an early age may prevent metabolic abnormalities.

Keywords: Obesity■Metabolically healthy■Metabolically unhealthy■Children■Adolescents

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http://dx.doi.org/10.1016/j.jnma.2017.02.008

INTRODUCTION

Obesity is still on the rise worldwide.[1] In the United States, the prevalence of obesity remains high.[2] In 2011–2012, the prevalence of obesity in American youth was 16.9%,[2] while 27% of high school students in New York City are obese.[3] Obesity is an independent risk factor for cardiovascular disease with well-known association with co-morbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus.[4,5] A unique subset of obese individuals, known as "metabolically healthy obese" (MHO), however do not have any metabolic co-morbidities.[6] Long-term follow-up studies in adults have shown that such individuals are not at increased risk of developing cardiovascular disease compared with healthy non-obese and are at lower risk compared with metabolically unhealthy obese (MUO) subjects.[4,7–9] However, the complexity of what keeps some obese individuals healthy has not been clearly identified. Especially in youth, the MHO subtype has not been well studied and it is a challenge for physicians to differentiate such individuals from those at higher risk. Understanding the differences of obesity subtypes may be useful in efficiently guiding prevention and treatment strategies.

The purpose of this study was to identify MHO and MUO children and adolescents with respect to metabolic factors with the aim to find the predictors of MHO subtype in our study population. In adults, central obesity has been shown to be associated with unfavorable metabolic profile and higher risk of cardiovascular disease.[10–12] We hypothesize that the MHO children and adolescents are younger and have lower waist circumferences than MUO children.

METHODS

A retrospective chart review was completed for pediatric patients with BMI ≥95th %tile for age and gender, seen by Pediatric Endocrine service at State University of New York Downstate Medical Center (SUNY DMC) and Kings County Hospital Center (KCHC) between July 2014 and June 2015. All patients had waist (at the top of the iliac crest) and hip (maximum of buttocks) circumferences measured during their clinic visits by pediatric endocrinologists.[13] Anthropometric and blood pressure (BP) measurements were obtained from the same clinic visit. Fasting laboratory tests were done within six months of the visit. Data including demographics, physical examination findings, laboratory results, family history, and medical history were collected from retrospective chart review of the patients' medical records. Height, weight, and BMI % tiles and z-scores (based on 2000 CDC growth charts) were obtained.[14] Insulin resistance index (HOMA-IR) was calculated using the formula: fasting plasma glucose (mg/dl) times fasting serum insulin (mU/l) divided by 405.[15] The study received approval from SUNY DMC and KCHC institutional review boards.

Definition of obesity subtypes

The patients were divided into two groups: MHO and MUO. MUO was defined as meeting one or more of the following criteria: fasting plasma glucose ≥100 mg/dl, HbA1c > 5.6%, BP ≥ 90th %tile for age, sex and height, TG ≥ 150 mg/dl, or HDL <40 mg/dl. MHO was defined as meeting all of the following criteria: fasting glucose <100 mg/dl, HbA1c ≤ 5.6%, BP < 90th %tile for age, gender and height, TG level <150 mg/dl, and HDL ≥40 mg/dl. Age and gender specific %tile values for systolic and diastolic BP were based on the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents from the National Heart, Lung, and Blood Institute.[16] The HbA1c cut-off of >5.6% as well as the fasting plasma glucose cut-off of ≥100 mg/dl were based on American Diabetes Association recommendations for prediabetes and impaired fasting glucose respectively in children and adolescents.[17] TG and HDL cut-offs (TG ≥ 150 mg/dl and HDL < 40 mg/dl) were based on International Diabetes Federation recommendations in children and adolescents.[18]

Statistical analysis

T-tests and chi-squared tests were used to compare the continuous and categorical variables respectively. $P < 0.05$ was considered statistically significant. The necessary sample size for each group to detect a medium effect size ($d = 0.5$) at power of 0.80 was 64.[19] Odds ratios with 95% CIs were calculated for significant predictors of MHO phenotype obtained from the t-tests and chi-squared tests. The significant predictors obtained from all the above tests were entered into the stepwise logistic regression model. HOMA-IR and fasting insulin levels, although significant on t-tests, were not included in the stepwise logistic regression analysis due to a large number of missing values for both variables in the collected data. The variables used for defining the MUO phenotype were not used in the regression analysis. Hosmer and Lemeshow test was used to assess whether the regression model fit the data. Data are expressed as mean ± SD unless otherwise noted.

RESULTS

A total of 189 patients, ages 4−19 years, were included, of which 118 (62.4%) were classified as MUO and 71 (37.6%) as MHO. Almost 99% of the subjects were of African−American or Caribbean descent. The MHO group comprised of 58% (n = 41) females and 42% (n = 30) males while the MUO group comprised of 47% (n = 55) females and 53% (n = 63) males. The two groups were similar with respect to the gender distribution ($p < 0.13$). The MHO subjects were significantly younger with mean age of 11.6 ± 3.3 years versus MUO who had a mean age of 12.9 ± 3.2 years ($p < 0.009$). The MHO group had less pubertal advancement with lower Tanner staging than the MUO group ($p < 0.03$). The median Tanner stage for MHO group was 3 while that of MUO was 4. The MHO group had lower BMI and BMI %tile, smaller waist and hip circumferences, lower fasting insulin, and HOMA-IR values. With age adjustment, BMI, BMI %tile, and waist and hip circumferences remained significantly different between the two groups. MHO subjects were also less likely to have acanthosis nigricans than the MUO (80% vs 93%, $p < 0.005$). The clinical characteristics of the two groups are shown in Table 1. The two groups were not significantly different with respect to height %tile and weight %tile, electrolytes, liver functions tests, total white blood cell (WBC) count, platelet count, vitamin D levels, thyroid function tests, total cholesterol, and LDL levels.

For all the significant variables in Table 1, the likelihood for being in the healthy group was calculated as shown in Table 2. Older age, increased waist and hip circumferences, higher BMI %tile, higher fasting serum insulin levels and HOMA-IR values as well as the presence of acanthosis nigricans decreased the odds of being MHO. The significant adiposity variables (BMI %tile, waist circumference, and hip circumference) and presence of acanthosis nigricans along with age and gender were entered into the stepwise regression analysis model. Only age and BMI %tile remained significant predictors of MHO phenotype in the stepwise regression analysis (Table 3). One-year increase in age reduced the odds of being healthy by 16%. One-unit increase in BMI percentile reduced the odds of being healthy by 29%.

When adjusted for age, gender, and BMI, no significant differences of the variables were found between the two groups (height %tile, $p = 0.452$; weight %tile, $p = 0.794$; Tanner stage, $p = 0.213$; waist circumference, $p = 0.284$; hip circumference, $p = 0.056$; presence of acanthosis nigricans, $p = 0.106$; fasting insulin level, $p = 0.122$; HOMA-IR, $p = 0.119$; WBC count, $p = 0.856$; platelet count, $p = 0.136$; Vitamin D level $p = 0.694$).

DISCUSSION

There is no standard definition of MHO and several different criteria have been used in literature, explaining the varying prevalence rates of MHO.[20] Primeau et al reported MHO prevalence ranging from 18 to 44% from a review of 15 studies that used different MHO criteria and studied different gender/ethnic groups.[21] From the data obtained from the U.S. National Health and Nutrition Examination Survey (NHANES) (1998−2004),