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PRESENCE OF THE METABOLIC SYNDROME (MS) IN OBESE ADOLESCENTS PREDICTS IMPAIRED GLUCOSE TOLERANCE (IGT) AND NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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Abstract

Purpose—To evaluate whether the presence of MS in obese adolescents is associated with other co-morbidities of obesity

Methods—85 obese teens with fasting insulin > 25 uU/ml and family history of type 2 diabetes mellitus and/or acanthosis nigricans. Mean age 15.8 ± 1.7 years; body mass index 39.3 ± 6.6 kg/m2; 70% female; 54% Hispanic, 35% black. Laboratory analysis included fasting lipids, glucose, gamma gluteryl transferase (GGT), and oral glucose tolerance testing. Additional liver transaminases and liver ultrasound (US) were performed to evaluate presence and severity of fatty liver.

Results—All subjects met MS criteria for children for waist circumference; 49% for blood pressure; 54% for high density lipoprotein (HDL); 54% for triglycerides; 20% for impaired fasting glucose or impaired glucose tolerance (IGT). 47 subjects had 3 or more MS criteria. BMI was no different between groups with and without MS. Subjects with 3 or more MS criteria were more likely to have IGT ($p = .004$), elevated ALT ($p = .039$), elevated GGT ($p = .036$), fatty liver on US ($p < .001$), and more severe fatty liver ($p = .001$).

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Conclusions—Abnormal glucose regulation and evidence of non-alcoholic fatty liver disease (NAFLD) were more common in subjects meeting 3 criteria for MS than in those meeting fewer criteria. The identification of MS provides value to the primary care provider. Those patients meeting criteria for MS should be evaluated for glucose intolerance and NAFLD.

Keywords

metabolic syndrome; adolescent; non-alcoholic fatty liver disease; impaired glucose tolerance

Background

The metabolic syndrome (MS) in adults is associated with an increased risk for development of type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease. [1–4]

There are several definitions for MS in adults based on WHO (World Health Organization) and NCEP (National Cholesterol Education Program) criteria (table 1). [5–7] WHO criteria emphasize insulin resistance as the underlying etiology for MS whereas NCEP criteria emphasize clinical criteria. Most recently, additional modifications have been made by the International Diabetes Federation (IDF) as an attempt to make a “universal” definition. The usefulness of MS as a cluster of risk factors relative to each of the individual risk factors has been debated extensively in the adult literature.

Despite many attempts to define the MS in adolescents, diagnostic criteria have not been standardized. The use of different diagnostic criteria identifies different populations of adolescents, with some overlap. [8,9] Currently, the most widely used criteria for adolescents are the modified Cook criteria (table 1). [10]

It is likely that certain features of the MS are closely linked to future risk of development of other diseases associated with insulin resistance, such as T2DM or non-alcoholic fatty liver disease (NAFLD). One study followed a subset of 77 children and adolescents for 2 years. Importantly, all 8 subjects who developed diabetes during the 2-year follow-up period had impaired glucose tolerance (IGT) at baseline. [11] Non-glucose parameters can also be predictive of glucose abnormalities. For example, a previous study from our group demonstrated that elevated fasting triglycerides > 150 mg/dl, one of the adult criteria for MS, is associated with IGT in a population of obese, insulin-resistant adolescents. [12]

NAFLD occurs frequently in obese youth. [13–15] In an Italian study of 75 obese children, 53% had evidence of fatty liver on ultrasound (US) and 25% had transaminases above the upper limit of normal. [16] Therefore, the relationship between insulin resistance and NAFLD in youth is important to understand. This is particularly true given the rising prevalence of obesity in the pediatric population and the need to develop simple screening tools to help identify those at risk for the development of diseases such as T2DM and NAFLD.

In pediatrics, the requirement for age and sex appropriate values makes the evaluation of risk factors more complicated for clinicians, and may lead to less frequent identification of the syndrome (table 1). The literature is limited with regards to the usefulness of identification of the metabolic syndrome in adolescents. Given that the diagnosis of MS is more complicated in this age group, the aim of this study is to determine whether diagnosis of the metabolic syndrome based on a fasting sample alone would be useful to clinicians in identifying patients at higher risk for co-morbidities of obesity.

Hypothesis

Obese adolescents with 3 or more MS criteria are more likely to have other co-morbidities of obesity, such as abnormal glucose regulation and NAFLD than those with fewer criteria.

Methods

Subjects

Approximately 200 patients within an inner city healthcare system which serves a largely Hispanic and black population of indigent patients in Denver county with risk factors for the development of T2DM were pre-screened for study eligibility; 116 met eligibility criteria [elevated fasting insulin level > 25uU/ml or HOMA-IR > 3.5 (Homeostasis model assessment of insulin resistance: fasting insulin in mU/l multiplied by fasting glucose in mmol/l divided by 22.5).] [17] 54% of eligible patients (N = 63) were enrolled in the study. The remaining 22 subjects were recruited from the local children's hospital. Eighty-five adolescents ages 12–20 years with at least 2 risk factors for the development of diabetes (BMI > 30 or > 95% for age, family history of T2DM, or acanthosis nigricans) AND biochemical evidence for insulin resistance were enrolled.

Exclusion criteria included pre-existing diabetes at the time of study enrollment, pregnancy, significant heart disease, admitted excessive alcohol use, liver dysfunction as evidenced by ALT > 3x the upper limit of normal or kidney dysfunction as evidenced by serum creatinine > 1.5 mg/dl. Subjects were part of a randomized intervention study using metformin; this study uses baseline data from the study population.

This study protocol was approved by the Institutional Review Board and written patient and parental consent (for subjects under 18 years of age) was obtained at the time of enrollment in the study. This cohort of subjects has been previously reported. [12]

Protocol

Recruited subjects were instructed to fast overnight for a minimum of 9 hours before presenting for the study visit. A blood sample was obtained for serum glucose, insulin, and lipid panel (total cholesterol, HDL and LDL and triglycerides) as well as a GGT (gamma-glutamyl transpeptidase) to evaluate for possible excessive alcohol intake. In order to evaluate the presence of markers for NAFLD, the last consecutive 49 subjects also had additional liver function tests including AST (aspartate aminotransferase) and alanine aminotransferase (ALT). The upper limit of normal for ALT for the lab was 65 IU/l, AST 30 IU/L and GGT 55 IU/L. Subjects were excluded if the ALT was greater than 3 times the upper limit of normal. Subjects with ALT 1.5–3x the upper limit of normal had further evaluation including repeat liver transaminases, hepatitis B surface antigen, hepatitis C antibody, ceruloplasmin, alpha-1 antitrypsin level or phenotype, prothrombin time, iron, TIBC and ferritin, and anti-nuclear antibodies. If this evaluation did not identify another etiology for liver dysfunction, subjects were presumed to have NAFLD. No underlying liver disease was identified in any subjects. 37 subjects had a liver US performed and of sufficient quality to assess for the presence or absence of fatty liver. The USs were read by a single blinded radiologist and scored for severity of fatty liver, with 0 = no fatty liver, 1 = mild fatty liver, 2 = moderate fatty liver, and 3 = severe fatty liver. [18,19] Subjects with an US reading of 1, 2 or 3 were considered to have NAFLD.

Subjects then received a 75-gram glucose challenge and repeat serum glucose determination was obtained 2 hours later. BMI, blood pressure (BP), waist circumference (measured at umbilicus) and demographic information were collected. Modified Cook's criteria MS in adolescents were used to determine the number of MS criteria present.

Statistical analysis

Demographic variables were compared between the two groups (1–2 MS criteria vs. 3 or more MS criteria). Chi-square test was used, or Fisher's exact test if 50% of the cells in the contingency table had expected counts less than 5, to test for the categorical variables such as gender, race, and presence or absence of impaired glucose tolerance, abnormal transaminases, or abnormal liver ultrasound. P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS/PC (version 14; 2006).

Results

The mean age was 15.8 ± 1.7 years. The mean BMI was 39.3 ± 6.6 kg/m^2, range 27.9–55 kg/m2. The study population was 70% female, with 54% Hispanic, 35% black, 5% white, 5% American Indian, and 1% Asian. Ten subjects were missing blood pressure data. In 2 subjects, this missing data impacted whether the subject was in the 1–2 MS criteria group vs. the 3 or more MS criteria group, so those 2 subjects were removed from the analysis.

All subjects met MS criteria for elevated waist circumference. The number of subjects meeting other MS criteria is listed in table 2.

Ten subjects meeting 3 or more MS criteria had IGT (p = 0.004), while no subjects with less than 3 MS criteria did. (Table 3) Fatty liver by US was present in 73% of subjects. Elevated ALT (p = 0.039), elevated GGT (p = 0.036), and fatty liver on US (p < 0.001), were significantly more common in subjects meeting 3 or more MS criteria. (Table 3) In addition, fatty liver severity was significantly greater in subjects meeting 3 or more MS criteria (p = 0.001). Subjects with morbid obesity (BMI > 40 kg/m2) showed a trend towards greater prevalence of meeting criteria for MS, although half of subjects with BMI < 40 kg/m2 also met criteria. Fasting insulin (42.8 ± 4 vs. 29.1 ± 3.7 uU/mL, p=0.015) and triglycerides (161±15 vs. 119.6 ± 12 mg/dL, p=0.037) were significantly higher in subjects with steatosis on US, while HDL was significantly lower in subjects with steatosis (38.8 ± 1.3 vs. 43.9 ± 1.8 mg/dL, p<0.03).

Discussion

In this population of obese, insulin resistant adolescents, we indeed found that the presence of the MS was associated with an increased prevalence of IGT and markers for NAFLD. Presence of the MS using the modified Cook definition was extremely common in subjects with morbid obesity (BMI > 40 kg/m2) but was also present in more than half of these obese adolescents with a BMI < 40 kg/m2. Since all of these obese subjects met waist circumference criteria for MS, adolescents with the presence of 2 or more additional MS criteria were significantly more likely to also have abnormal glucose regulation and evidence of more severe NAFLD. Of concern, even of subjects without evidence of MS, nearly half had evidence of NAFLD, either ALT > 40 U/l or fatty liver by US.

Since all of our subjects were obese, waist circumference was not helpful in differentiating subjects with increased risk of co-morbidities. However, elevated waist circumference may be helpful in the overweight category, where athletes with increased muscle mass may be incorrectly identified as overweight by BMI criteria alone. A study of waist circumference in 6–13 year old children showed that only 28% of children with BMI 85–95% have a waist circumference > 90%, compared to 87% of those with a BMI > 95%. [20] A large study of almost 2000 children in Greece showed waist circumference to be the most significant predictor for cardiovascular disease risk factors (total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and blood pressure). [21] Another study of 2597 American youth showed that within a given category of weight, subjects with high waist circumference were more likely to have elevated triglycerides, elevated insulin

levels, and the MS than those in the low waist circumference group in the same weight category. [22] A recent Australian study did not find waist circumference at age 8 years to be helpful in predicting metabolic risk at age 15. [23] Thus, although universal measurement of waist circumference is unnecessary, measuring waist circumference may be a useful part of the assessment in the subgroup of muscular adolescent athletes with BMI in the 85–95% range. Reference values are available for 90% cut-offs for waist circumference in European-American, African-American and Mexican-American adolescents. [24]

Although obesity has been shown to be a risk factor for NAFLD in adults, [25] insulin resistance appears to be even more tightly correlated with NAFLD. An Italian study of 46 adults with NAFLD showed insulin resistance to be the strongest predictor of NAFLD, with fasting insulin levels nearly twice as high in patients with NAFLD as in controls. [26,15] NAFLD is also associated with an elevated serum triglycerides [27,28], low HDL-C [27], abnormal glucose regulation [29], and central adiposity [27], all features of the metabolic syndrome. A study of 30 non-obese adults with NAFLD and normal glucose tolerance showed these subjects to have significant insulin resistance and features of the MS, again implicating insulin resistance, even without obesity. [30] In our study population, all subjects had evidence of insulin resistance, which may explain the high rates of NAFLD even in those subjects without the MS.

As IFG or IGT are combined as one of the 5 MS criteria, IGT in this study is a component of the diagnosis of MS and also is an outcome measure. If we focused only on results available from the baseline fasting sample to diagnose the MS, 6 of the 7 subjects with IGT alone still met 3 or more criteria for the metabolic syndrome. When the data are analyzed with that one subject changing categories (from 3 or more to < 3 criteria), MS as defined by fasting laboratory values alone is still predictive of IGT ($p = 0.019$).

Elevated ALT and fatty liver on liver US, while not the gold standard for diagnosis of NAFLD, can provide non-invasive evidence of NAFLD, limiting liver biopsies in pediatric patients. [31] US has been shown to identify fatty liver with a sensitivity of 89–95% and a specificity of 84–93%. [32] Current NAFLD literature uses a cut-off for ALT of 40 U/l to define elevated ALT. [14,27]. However, clinical laboratories have different cut-offs for the upper limit of normal for ALT as well as other laboratory markers of NAFLD. Using the cut-off of 40 U/l for ALT rather than the upper limit of normal for our laboratory improved the predictive value of 3 or more MS criteria for identifying elevated ALT, however this did not reach statistical significance. ROC curves were used to determine which cut-off for ALT was associated with metabolic syndrome in our population; presence of the metabolic syndrome was associated with an ALT > 35 U/l. Of 5 black subjects with ALT > 40 U/l, only 2 had fatty liver on US. No black subjects had ALT above the upper limit of normal for our laboratory. In contrast, of 17 Hispanic subjects with ALT > 40 U/l, 13 (76%) had fatty liver on ultrasound. Previous research has shown a decreased prevalence of NAFLD in black obese children. [33]

Presence of the MS was associated with an increase in fatty liver on US, as well as in increase in ALT and GGT. The majority of the NAFLD literature reports elevated ALT as more highly associated with NAFLD than GGT. In our subjects however, the presence of MS predicted elevated GGT as well as ALT. A large Italian study of obese adults also showed elevated GGT to be associated with elevated triglycerides and hyperglycemia. [34]. In addition, a study of severely obese adults undergoing bariatric surgery showed a decrease in GGT to be the best predictor of improvement in inflammation, fibrosis, and non-alcoholic steatohepatitis (NASH). [35]

Limitations

This group of adolescents was selected for insulin resistance, thus these results may be different in unselected obese adolescents. In addition, surrogate markers were used to measure insulin

sensitivity, rather than a gold standard such as an insulin clamp. Many of the MS criteria vary depending on race and ethnicity. The subjects in this study were largely Hispanic and black, therefore the results may be different in other racial groups. Subjects with ALT > 3 times the upper limit of normal were excluded, therefore our results may underestimate the prevalence of NAFLD in youth with the MS, although the one subject initially excluded for ALT was confirmed to have NAFLD by biopsy and later enrolled in the study after his ALT improved. In addition, undocumented alcohol use could have contributed to GGT elevations. Finally, not all of our subjects had ultrasounds available for analysis and US itself is not the most sensitive tool for assessing fatty liver, especially in severely obese subjects. However, due to the young age of the subjects, US is preferable in avoiding the risk of biopsy or radiation exposure associated with CT scans, and allows shorter imaging times when compared with magnetic resonance imaging.

Practice implications

In the pediatric population, identification of MS based on fasting results should lead the provider to monitor patients more closely for abnormal glucose regulation and NAFLD. Patients with extreme abnormalities in individual MS criteria (for example, triglycerides > 400 mg/dl or severe hypertension) should be evaluated and treated as necessary. Separate from the importance of individual components, the diagnosis of MS may have several beneficial effects. The diagnosis of MS may facilitate identification by the primary care provider of abnormal glucose regulation or NAFLD. These diagnoses may lead the provider to consider additional treatment modalities beyond what would likely be used for obesity alone. Early identification and intervention for these disorders may minimize long term morbidity and mortality. In addition, patients and/or parents may be more likely to make significant lifestyle changes if there is a specific diagnosis rather than just being told that they are overweight.

In contrast, in this era of cost containment, obese patients without evidence of the MS may require less frequent monitoring for abnormal glucose regulation, especially if they do not continue to gain weight over time. Future research should assess longitudinal risk of development of insulin resistance related co-morbidities in obese youth with and with out the MS.

Conclusions

In this group of insulin-resistant, obese adolescents, the presence of multiple MS criteria was associated with a significantly higher incidence of IGT and markers for NAFLD. The presence of MS provided a measure of risk above and beyond elevated BMI and waist circumference.

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Table 1

comparison of different metabolic syndrome criteria

	WHO criteria Insulin resistance or altered glucose metabolism plus 2 or more additional criteria:	**Modified NCEP criteria 3 or more of:**	**IDF criteria Elevated waist circumference plus 2 or more additional criteria:**	**Modified Cook criteria for adolescents 3 or more of:**
Obesity or abdominal obesity	BMI > 30 kg/m^2 and/or waist/hip ratio > .9 male/.85 female	Waist circumference > 102 cm male > 88 cm female	Waist Circumference > 94 cm male > 80 cm female	BMI or Waist circumference > 95% for age and sex
Blood Pressure	> 140/90 mg Hg	> 130/85	> 130/85	> 90% for age, sex and height
Triglycerides	> 150 mg/dl	> 150 mg/dl	> 150 mg/dl	> 110 mg/dl
HDL	< 35 mg/dl male < 39 mg/dl female	< 40 mg/dl male < 50 mg/dl female	< 40 mg/dl male < 50 mg/dl female	< 40 mg/dl
Glucose other	Microabuminuria > 20 mg/min	Fasting glucose > 100 mg/dl	Fasting glucose > 100 mg/dl 2-hour glucose > 140 mg/dl OR diagnosed diabetes	Fasting glucose > 100 mg/dl 2-hour glucose > 140 mg/dl OR diagnosed diabetes

Table 2

Subjects meeting specific Modified Cook metabolic syndrome criteria

	# meeting criteria
Waist circ > 95% for age and sex	83 (100%)
Elevated BP > 90% for age, sex and height	37 (49%)
Low HDL (< 40 mg/dl)	45 (54%)
Elevated triglycerides (> 110 mg/dl)	45 (54%)
IFG or IGT*	17 (20%)
Fasting glucose > 100 mg/dl	7 isolated IFG
2-hour glucose > 140 mg/dl	7 isolated IGT
	3 IFG and IGT

* IFG: impaired fasting glucose; IGT: impaired glucose tolerance

Table 3

characteristics of subjects with and without >/= 3 MS criteria

	1–2 MS Criteria N = 36	>/3 MS Criteria N = 47	P value
BMI (kg/m2)	38.9	39.6	**NS**
BMI < 40 (N = 50/83)	26 (72%)	24 (51%)	.05
BMI > 40 (N = 33/83)	10 (28%)	23 (49%)	.05
IFG ≥ 100 mg/dl (N = 10/83)	0 (0%)	10 (21%)	**.003***
IGT ≥ 140 mg/dl (N = 10/83)	0 (0%)	10/47 (21%)	**.004***
GGT ≥ 55 (N = 10/77)	1/34 (3%)	9/43 (21%)	**.036***
ALT ≥ 65 U/l (N = 8/51) **ALT ≥ 40 U/l** (N = 27/51) **ALT ≥ 35 U/l** (N = 37/51)	1/21 (5%) 8/21 (39%) 12/21 (57%)	7/30 (23%) 19/30 (63%) 25/30 (83%)	.119 08 **.039***
Fatty liver by US (N = 27/37)	8/17 (47%)	19/20 (95%)	**< .001***
Fatty liver score (N = 37)	.93 (SD 1.6)	2.2 (SD .95)	**.001***

* statistically significant > p = .05