Relationship between Carotid Intima-Media Thickness and Metabolic Syndrome in Adolescents

Thomas Reinehr, MD[1], Rainer Wunsch, MD[2], Carolin Pütter, MD[3], and André Scherag, PhD[3]

Objective To test the hypothesis that metabolic syndrome (MetS) is more predictive of carotid intima-media thickness (IMT) than the sum of the individual components of MetS.

Study design We analyzed the relationships between 2 definitions of the MetS and IMT in 461 overweight adolescents aged 10-18 years (median body mass index, 28.6 kg/m^2). We used regression models and receiver operating characteristics (ROCs) for increased IMT (defined as ≥0.7 mm).

Results The prevalence of MetS was 15.0% and 26.9% according to the 2 definitions applied. At the group level, quantitative IMT was associated with body mass index, blood pressure, glucose levels at 2 hours in an oral glucose tolerance test, and with each of the MetS components (all $P < .05$). At an individual level, using the MetS definitions alone as a diagnostic test for the presence of increased IMT (area under the ROC curve, 0.60-0.66) was inferior when compared with the sum of all individual components (area under the ROC curve, 0.65-0.85). Adding the presence or absence of MetS to the components did not improve the accuracy.

Conclusion Overweight adolescents with MetS demonstrated increased IMT values compared with overweight adolescents without MetS. The best model for diagnosing increased IMT was the sum of the quantitative components of MetS. The use of dichotomized variables reduced the diagnostic accuracy. Thus, in clinical practice, treatment of overweight adolescents should be based on weighing cardiovascular risk factors themselves, rather than on the dichotomous variable MetS. *(J Pediatr 2013;163:327-32)*.

See editorial p 314

Obesity in childhood and adolescence is associated with various cardiovascular risk factors, including hypertension, dyslipidemia, and impaired glucose metabolism.[1] This cluster of risk factors is known collectively as the metabolic syndrome (MetS).[2] The concept of MetS is that this cluster of risk factors is predictive of cardiovascular disease beyond the risks associated with the syndrome's individual components.[2-4]

The concept of MetS is controversial. Mente et al[5] reported underestimation of the risk of myocardial infarction in adults using the dichotomous variable MetS instead of the continuous variables blood pressure and serum lipid levels. Other studies have reported no increased risk of MetS compared with the sum of its individual components based on carotid intima-media thickness (IMT) measurements in adults.[6,7] We recently analyzed the relationships between multiple definitions of MetS in children and IMT of the common carotid artery and found only a modest relationship between IMT and MetS in children.[8] Furthermore, a single cardiovascular risk factor, impaired glucose tolerance (IGT), predicted IMT better than any definition of MetS.

Prompted by these observations, we performed a more in-depth statistical analyses in a larger independent sample to study the relationship between IMT (as a surrogate measurement of outcome) and MetS. We analyzed the associations between different MetS definitions and IMT values using different statistical approaches including a model with all individual quantitative MetS components without dichotomizing, a model with all dichotomized MetS components, and models that included both individual quantitative MetS components and an indicator of when the definition of MetS was fulfilled.

Methods

The local Ethics Committee of the University of Witten/Herdecke approved this study. Written informed consent was obtained from all subjects and their

AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
HDL	High-density lipoprotein
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
IMT	Intima-media thickness
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
ROC	Receiver operating characteristic

From the [1]Departments of Pediatric Endocrinology, Diabetes, and Nutrition Medicine, [2]Pediatric Radiology and Ultrasound, Vestische Hospital for Children and Adolescents Datteln, University of Witten/Herdecke, Witten/Herdecke, Germany; and [3]Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany

The authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT00435734.

 http://dx.doi.org/10.1016/j.jpeds.2013.01.032

parents. We collected clinical data and data on cardiovascular risk factors from 461 apparently healthy overweight adolescents, aged 10-18 years, who presented consecutively at the outpatient obesity clinic at Vestische Hospital for Children and Adolescents Datteln. None of these adolescents had been included in any previous study of IMT measurements.[8] All of the adolescents were Caucasians. Adolescents with an endocrine, genetic, or metabolic disorder or receiving medical therapy were excluded from this study.

Overweight was defined according to the criteria of the International Obesity Task Force using German population-based reference data.[9,10] The degree of overweight was quantified using the Cole least mean squares method, which normalizes the body mass index (BMI)-skewed distribution in childhood and expresses BMI as an SDS (BMI-SDS).[11]

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured to the nearest 0.1 kg with the child wearing only underwear, using a calibrated balance scale. Waist circumference was measured halfway between the lower rib and the iliac crest.[12]

Pubertal stage, classified according to the definitions of Marshall[13] and Tanner,[14] was determined by well-trained physicians. Pubertal developmental stage was categorized into 3 groups based on breast and genital stages (prepubertal: boys at genital stage I, girls at breast stage I; midpubertal: boys at genital stage II-III, girls at breast stage II-III; late/postpubertal: boys at genital stage ≥IV, girls at breast stage ≥IV). This classification scheme was used because insulin resistance as a potential driver of MetS increases physiologically during midpuberty and decreases at the end of puberty.[15]

Triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol, and glucose concentrations were measured in the fasting state using commercially available test kits (HDL-C Plus and LDL-C Plus, Roche Diagnostics, Mannheim, Germany; Vitros analyzer, Ortho Clinical Diagnostics, Neckargemuend, Germany; MEIA, Abbott, Wiesbaden, Germany). An oral glucose tolerance test was administered in accordance with published guidelines.[16] IGT was defined as a 2-hour serum glucose level >140 mg/dL on an oral glucose tolerance test. Impaired fasting glucose was defined as fasting serum glucose level ≥100 mg/dL.

Blood pressure was measured according to the guidelines of the National High Blood Pressure Education Program.[17] Systolic and diastolic blood pressures were measured twice in the right arm after a 10-minute rest in the supine position using a calibrated sphygmomanometer, and the 2 values were averaged. Elevated blood pressure was defined as average blood pressure above the 95th percentile for height, age, and sex.[17]

MetS was defined using the criteria of Weiss et al[18] (BMI >97th percentile plus 3 or more of the following: elevated blood pressure, triglycerides >97th percentile, HDL-cholesterol <5th percentile, and IGT) and the International Diabetes Federation (IDF)[3,19] (waist circumference >90th percentile plus 2 or more of the following criteria: impaired fasting glucose, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and HDL-cholesterol <40 mg/dL). The 97th percentile value for triglycerides is 110 mg/dL and the 5th percentile value for HDL-cholesterol is 40 mg/dL in apparently healthy German adolescents.[20] We used German percentiles for waist circumference.[12]

One investigator, blinded to the participants' cardiovascular risk factor status, measured carotid IMT by B-mode ultrasound using a 14-MHz linear transducer following a standardized protocol. Measurements were performed at the common carotid artery near the bifurcation at the far wall after a 10-minute rest. The sonographer performed 4 measurements on each side and took the maximum value for statistical purposes, because the strongest associations between the different measurements of IMT and coronary risk factors are achieved by using the maximum value, not the mean value, of IMT.[21,22] Measurements were made with the patient supine with the head turned slightly to the side. The intraobserver coefficients of variability of IMT measurements were 6% for IMT of 0.4 mm and 4% for IMT of 0.7 mm.[8,22] We used the top quartile of IMT measurements (≥0.7 mm) to define increased cardiovascular risk.

At the group level, we used standard descriptive and exploratory inferential statistics to display sample characteristics. We fitted univariate and multiple logistic regression models adjusted for sex, pubertal stage, and age for the dichotomized IMT outcome (IMT at or above the top quartile of IMT vs IMT below the top quartile of IMT) and for the quantitative MetS components as predictors: BMI, waist circumference, systolic and diastolic blood pressure, triglycerides, HDL-cholesterol, fasting glucose, and glucose tolerance. In addition, LDL-cholesterol and triglycerides:HDL-cholesterol were evaluated. All quantitative variables were entered as linear predictors; no automatic variable selection algorithm or no transformations were applied. We then ran similar (sensitivity) analyses for alternative IMT cutoffs and quantitative IMT outcome values using linear regression while graphically checking for nonlinear relationships (**Figure 1**; available at www.jpeds.com).

We defined the dichotomized IMT outcome as the gold standard (IMT at or above the top quartile of IMT [positive] vs IMT below the top quartile of IMT [negative]), and fitted 5 different models for each of the 2 MetS definitions: (1) all individual quantitative MetS components; (2) all dichotomized MetS components; (3 and 4) included an indicator of the definition of MetS in addition to the factors of in models 1 and 2; and (5) only the indicator of MetS. We used receiver operating characteristics (ROCs) to compare the performance of the diagnostic models. A numerical measure of the accuracy of a diagnostic model can be obtained from the area under the ROC curve (AUC), with an AUC of 1.0 indicating perfect accuracy and an AUC of 0.5 indicating that the model's predictions are no better than a random coin toss. Considering that the AUC tends to be larger in a given sample when more predictor variables are included, we report both the results in the total sample and the summary results if the sample was randomly split into training (to build the model) and test