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The Influence of Metabolic Syndrome Risk Factors on Carotid Intima Media Thickness in Children

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Abstract

Pediatric obesity is a major health concern today, which pre-disposes individuals to metabolic syndrome (MS), and the risk of premature cardiovascular disease (CVD). Use of carotid intima media thickness (CIMT) is recognized as non-invasive way to assess vascular health. The objective of this study was to determine which MBS risk factors has an influence on increasing one's risk of an increased CIMT in children. In southern Maine 189 children (age: 10.52 ± .52 years) had their MBS risk factors and CIMT assessed. Based on CIMT, children were divided into quartiles and compared to MBS risk factors. Children in the highest quartile for CIMT had the highest waist circumference ($P < .05$) compared to all other groups, using a one-way analysis of variance. No other MBS risk factors had an influence on CIMT. It appears early identification of children with an elevated WC may be beneficial in identifying children at risk of premature CVD.

Keywords

metabolic syndrome, carotid intima media thickness, waist circumference, children

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Introduction

Cardiovascular disease (CVD) is the number one cause of death among adults in the United States, with coronary artery disease (CAD) representing the primary etiology.[1] A strong relationship exists between coronary artery disease (CAD) and metabolic syndrome (MetS). Those with MetS have an increased mortality risk due to accelerated atherosclerosis, leading to the development of CAD.[1-3] Currently one third of the U.S. adult population has MetS, which puts them at a 2 to 3 times greater risk of developing CVD, as well as 5 times greater risk of developing type II diabetes.[4] The prevalence of MetS has long eluded the scientific community due to the differing criteria used to define this syndrome. In an attempt to achieve some consensus, the Joint Task Force released a statement that from 1988-1994 to 2007-2012 the prevalence of MetS rose by more than 35% among US adults aged 18 years or older.[5] The Joint Task Force recognizes waist circumference (WC) as more indicative than BMI for identifying obese individuals at risk for MetS. It has been observed that individuals with excess body fat centrally located around the waist, otherwise known as android obesity, compared to excess body fat distributed to the hips, are at a higher risk of developing hypertension, insulin resistance (Type 2 diabetes mellitus), dyslipidemia, and MetS.[6]

Metabolic syndrome has traditionally been reported in adults. However, with the rise in pediatric obesity rates, MetS is now evident in adolescents. Although the medical community agrees on the risk factors associated with MetS and its impact on the health of the youth population, there has been a long-standing disagreement over the diagnostic criteria related to MetS in children and adolescence.[7-11] In fact, there are more than 40 definitions that have been reported for adolescent MetS.[12] Due to little consensus over what constitutes MetS in children, the prevalence is not clearly defined. In 2014, a

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cross-sectional study was conducted to compare the prevalence of MetS in adolescents using differing definitions. In a population size of 851 adolescents between 10 and 18 years of age, the prevalence of MetS was 0.9%, 3.8%, 4.1%, 10.5%, and 11.4%, according to the International Diabetes Foundation (IDF), Cook et al, Ford et al, Agudelo et al, and de Ferranti et al definitions, respectively.[8] With the current rise in adolescent obesity, the importance of accessing MetS in adolescents should be of more importance in our society, due to the adverse health effects seen in adults with MetS, such as premature CAD, and Type II diabetes mellitus.[13]

Carotid intima media thickness (CIMT) is widely known as a predictor for atherosclerotic plaque development that may lead to coronary artery disease. The greater the CIMT thickness, the greater risk of developing atherosclerotic coronary artery disease (ACAD).[14,15] A study conducted in Turkey looked at 3 groups of individuals, those with no ACAD, those with single vessel ACAD and those with multi vessel ACAD. As the severity of ACAD increased, so did the individual's CIMT.[16] Amato et al[17] demonstrated that the presence of a CIMT $>$ 1 mm was associated with a 7-fold increased risk of having significant coronary stenosis. Although data on how MetS influences CIMT is relatively scarce, the Bogalusa Heart Study (BHS), assessed the association between MetS and CIMT in young non-diabetic adults with a mean age of 32 ± 3 years. Based on the criteria from 2 different governing bodies for MetS, as CIMT increased in the BHS, the prevalence of MetS also increased. Those in the highest quintile of CIMT were at a 3 to 4-fold increased likelihood of having MetS, suggesting that those with MetS were at an increased risk of future cardiovascular events.[18]

Many of the risk factors associated with MetS, specifically obesity, are lifestyle related. It has been observed that in obese individuals that are put on a 1-year intervention of physical exercise, nutrition education and behavior therapy, a significant decrease was seen in insulin resistance, blood pressure, triglycerides, and CIMT, while at the same time seeing a significant increase in HDL-C.[19] Thus, lifestyle modifications have the ability to positively influence children's metabolic and cardiovascular health. Irrespective of what definition is used to define Mets in adolescents, they all use the same variables. Therefore the purpose of this study is to determine which MetS risk factors have the greatest influence on a child's CIMT and thus their cardiovascular health.

Methods

This study was conducted through the Cardiovascular Health Intervention Program (CHIP) and is a collaborative program between the University of New England (UNE) and local public schools. The subject pool consisted of 5th grade children who attended elementary schools in southern Maine during the spring of 2016 and 2017.

Following approval from the superintendent of each school system, the CHIP personnel met with each individual school principal and their 5th grade teachers to explain the program, obtain approval and determine screening dates. Prior to the screening date, a 15 to 20 minute presentation was given to the students to explain the importance of cardiovascular health and an overview of the CHIP. A packet was given to each child that contained a cover letter explaining the program along with a medical history form, a consent form and an assent form. The packets were collected and the data from the family and student's medical history was entered into a secured university website prior to the screening date. Prior to the screening dates, university students were trained in the assessment of CAD risk factors, and appropriate ways in which to communicate with 5th grade children.

When the children arrived to the university from their schools, they were given a brief explanation of the different screening stations. The screening stations for assessing risk factors were in the order as follows: (1) blood lipids and glucose; (2) anthropometric assessment; and (3) resting blood pressure (BP). In addition, a random sample of normal and overweight/obese children completed an ultrasound scan of their right and left carotid artery to determine carotid intima media thickness at their school.

An individual report of children's cardiovascular profile was sent home for the parent(s) or guardian to review. Within the letter, recommended healthy values were provided with information on healthy lifestyle changes that could have a favorable influence on their risk factor profile. The parents of the children were also encouraged to seek further advice from their family physician if the values were out of the normal range during their next scheduled appointment.

Screening Stations

Blood Lipids and Glucose Collection Station

The night before screening, the children were asked to complete a 12 hours fast so an accurate measurement could be completed with respect to blood lipid and glucose profiles. To verify the children were fasting, they were asked if they had anything to eat or drink other than water in the past 12 hours. If a child was in a non-fasting state, they were not included in this data set. A capillary tube of blood was obtained using the fingerstick method and analyzed using a calibrated Cholestech LDX cholesterol analyzer based on recommendations by Cholestech Corporation (Cholestech Corporation, Hayward CA). The lipid/glucose panel included HDL-C, triglycerides, and blood glucose.

Anthropometric Assessment Station

Waist circumference was measured using a Gulick tape measure by having the children standing, arms at sides, feet together, and abdomen relaxed. Two horizontal measurements were taken at the height of the umbilicus and the average was recorded in centimeters (cm). If the measurements were not within 5 cm of each other a third measurement was taken and the median was recorded.

Resting Blood Pressure Assessment Station

An aneroid sphygmomanometer (Welch-Allyn Handheld Aneroid-Skaneateles Falls, NY) was used with appropriately sized cuffs for children to determine BP. Two BP measurements were taken 2 minutes apart from the right arm of each child after sitting quietly for 3 minutes. Systolic BP was recorded at the first appearance of a clear repetitive sound (Korotkoff Phase I) and diastolic BP was taken at the disappearance of repetitive sounds (Korotkoff Phase V). If the measurements were not within 6 mmHg of each other a third measurement was taken and the median recorded.

Carotid Intima-Media Thickness Ultrasound Assessment

On the scanning day, the same licensed sonographer performed all the ultrasound scans for consistency at the children's schools using the Terason t3200 ultrasound system and Terason 15l4 linear transducer probe. The ultrasound unit was calibrated to a dynamic range of 61, focal zone of 1, and focal range of 2. A depth from 3 cm to 6 cm was used to show clarity of the image. The hertz (Hz) ranged from 43 Hz to 22 Hz. All children were examined in the supine position with the neck extended and the head tilted slightly away from the side being examined. Once in position the child remained still for 1 minute, then the sonographer took two, 10 second scans of the far wall on the right and left carotid artery, 1 cm from the distal bulb.[20] The examinations were saved as a JPEG and then exported for further analysis.

Carotid Intima-Media Thickness (CIMT) Measurement

The Carotid Analyzer for Research Version 6 was used to measure the CIMT. The software was manually calibrated to 1 cm for each scan. The operator identified the area to measure 1 cm from the bulb, and a continuous 1-cm segment of the far wall. The software automatically detected intima-lumen and the media-adventitia interfaces and calculated average CIMT, with the minimum and maximum CIMT. Although there were 300 frames of ultrasound images, a minimum of 50 frames were analyzed with a confidence interval of 95% (difference of the maximum and the minimum less than or equal to .05 mm).

Table 1. Children's MetS Risk Factors (n = 189).

MetS risk factor	Mean	SEE
Triglycerides (mg/dl)	63.5	1.6
HDL-Cholesterol (mg/dl)	53.8	1.0
Glucose (mg/dl)	91.3	0.6
Waist circumference median (cm)	73.4	0.9
Systolic blood pressure (mm/Hg)	112.4	0.7
Diastolic blood pressure (mm/Hg)	73.4	0.7

Statistical Analysis

Subjects (n = 189) were divided into quartiles (Q1, n = 48; Q2, n = 37; Q3, n = 52; Q4, n = 52) based upon their average (right + left) CIMT value. A one-way analysis of variance was conducted using the following variables in relation to quartile group; triglyceride, HDL, Glucose, WC, Systolic Bp, Diastolic Bp. Post Hoc analysis for main effects were assessed using *T*-tests with Bonferroni adjustment. Significance was accepted at $P \leq .05$. Statistical analysis was completed using IBM SPSS V.24.

Ethical Approval and Informed Consent

The CHIP protocol was reviewed and approved by the institutional review board at University of New England (IRB# 20130917VISIP). Consent was voluntary and was given from the parents to participate and for their child to participate. In addition, assent was given from the child to participate. All 3 consent forms were required for the child to participate in the CHIP.

Results

A total of 189 children (age: 10.52 ± .52 years, weight: 47.34 ± 12.69 kgs, height: 148.13 ± 7.37 cm, 50% female) completed all measures of interest. To evaluate the effect of MetS on CIMT, the children were divided into 4 groups based upon averaging (left and right) CIMT. Due to no differences observed with left or right CIMT, the average of both are being reported. Following grouping of CIMT into quartiles it was determined through One-way ANOVA that each quartile was significantly different ($P < .05$) from each other for average CIMT. Analyses were completed with both boys and girls combined. Children's MetS risk factors can be seen in Table 1.

Table 2. MetS Risk Factors by Quartiles of CIMT (Mean ± SEE).

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
*WC (cm)	69.1 ± 1.8	70.7 ± 1.8	73.0 ± 1.7	79.7 ± 1.6
Triglycerides (mg/dl)	66.3 ± 3.4	60.84 ± 3.3	58.8 ± 2.7	67.5 ± 3.4
HDL-C(mg/dl)	54.9 ± 2.2	51.9 ± 2.0	55.3 ± 2.0	52.5 ± 1.8
SBP (mm/Hg)	111.2 ± 1.5	111.4 ± 1.3	111.5 ± 1.7	115.2 ± 1.4
DBP (mm/Hg)	71.9 ± 1.3	72.7 ± 1.3	74.3 ± 1.4	74.4 ± 1.3
Glucose (mg/dl)	89.3 ± 0.9	91.3 ± 1.0	92.1 ± 1.6	92.3 ± 1.2

*$P < 0.05$; Q1 versus Q4, Q2 versus Q4, Q3 versus Q4.

Table 2 represents the MetS risk factors by CIMT quartile. Of the different MetS risk factors, WC was shown to have an impact on CIMT. Children with the highest WC were found in Q4 (the highest mean CIMT) and was significantly different ($P < .05$) from all of the other quartile groups. There were no other differences observed with the other MetS risk factors across the different quartiles of CIMT.

Discussion

Approximately one fifth of the children in the United States are obese[7]; and children who are obese are at a greater risk of developing metabolic syndrome and thus the early development of atherosclerotic plaque buildup and premature CVD.[1-5] With heart disease being the number one cause of death in the United States, it is critical to identify those at risk at early age in order to implement specific interventions to reverse the physiological damage. Metabolic syndrome has been linked to increased likelihood of developing CAD and Type II diabetes mellitus, but many of the risk factors associated with MetS do not produce symptoms. Thus, encouraging lifestyles changes is a struggle for many physicians and health care providers. The unhealthy lifestyle choices established as a child has been observed to track into adulthood and can lead to a premature cardiovascular event if proper intervention at a young age does not take place.[21] The ability to access and see physical changes taking place in one's vessels at an early age could be very helpful to encourage healthy lifestyle changes. Carotid intima media thickness is widely known as a predictor for atherosclerotic plaque development that may lead to coronary artery disease and the use of ultrasonography to access CIMT is currently a non-invasive tool to access abnormal vascular changes. In respect to the relationship of MetS to CIMT in children, Toledo-Corral et al observed significantly higher values in CIMT in Latino children (11.0 ± 1.8 years) with persistent MetS (over a 3-year period) versus children without MetS, suggesting a relationship between CIMT and MetS. In respect to individual MetS risk factors, at baseline systolic blood pressure and 2-hour fasting glucose were independently significantly related to CIMT. At the time of CIMT the persistent MetS group WC and high blood pressure were associated with greater CIMT, though once controlled for total fat and lean tissue mass, they were no longer significant.[22]

The current findings suggest that a relationship exists between CIMT and WC in adolescents, but the mechanism to this relationship is still unknown. Very few studies have looked at how WC specifically influences CIMT in children. However, WC and BMI have been observed to be correlated to one another[23] and the association between BMI and CIMT is supported by Iannuzzi et al and White et al who observed that obese children had a larger CIMT than children with a healthy BMI.[24,25] In this current study, we have observed that of the MetS risk factors in United States (98% Caucasian) children, only WC appears to have a relationship with an adolescents CIMT. In comparison to Toledo-Corral et al there is agreement that WC (abdominal fat) is one of the primary variables that has a negative influence on CIMT. However, we did not observe BP to have an influence on CIMT, which may be related to our cross-sectional assessment versus longitudinal assessment over a 3 year period.

We recognize the importance of MetS as a diagnosis when trying to access vascular changes in adults, however when accessing children this may be of lesser importance when identifying their current physical vascular changes. This current research raises the question of the importance of diagnosing MetS in children, when it appears WC alone is the primary variable if one is looking to assess negative vascular changes. This has raised some concern in the medical community about the construct of MetS as a diagnosis for adolescents, rather than simply a cluster of individual cardio metabolic risk factors that can only be treated individually.[26]

However, of the variables of MetS in the current study, only WC appears to be associated with physical cardiovascular changes in a child's vasculature. Thus, the argument can be made that assessing a child's WC at annual pediatric checkups could be the most efficient way of determining a child's current cardiovascular health and implementing life style modifications that have been shown to positively influence all cardiovascular risk factors and decrease CIMT in children.[19] In addition, assessment of CIMT, through the use of ultrasound, should be considered for the purpose of prognosis. In conclusion, these findings continue to support early intervention of lifestyle modifications in treating childhood obesity and more specifically android obesity, which seems to have a relationship to an elevated CIMT in adolescents. Future longitudinal studies are needed to establish CIMT values in adolescents and to verify our current findings.

Author Contributions

All authors completed an active role in at least one part of the study, which included study design, data collection, statistical anaylysis and completing and reviewing of the manuscript.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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