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Adiposity has no direct effect on carotid intima-media thickness in adolescents and young adults: Use of structural equation modeling to elucidate indirect & direct pathways

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ABSTRACT

Background: Carotid intima-media thickness (cIMT) is associated with CV events in adults. Thicker cIMT is found in youth with CV risk factors including obesity. Which risk factors have the most effect upon cIMT in youth and whether obesity has direct or indirect effects is not known. We used structural equation modeling to elucidate direct and indirect pathways through which obesity and other risk factors were associated with cIMT.

Methods: We collected demographics, anthropometrics and laboratory data on 784 subjects age 10–24 years (mean 18.0 ± 3.3 years). Common, bulb and internal carotid cIMT were measured by ultrasound. Multivariable regression analysis was performed to assess independent determinants of cIMT. Analyses were repeated with structural equation modeling to determine direct and indirect effects.

Results: Multivariable regression models explained 11%–22% of variation of cIMT. Age, sex and systolic blood pressure (BP) z-score were significant determinants of all cIMT segments. Body mass index (BMI) z-score, race, presence of type 2 diabetes mellitus (T2DM), hemoglobin A1c (HbA1c) and non-HDL were significant for some segments (all $p = 0.05$). The largest direct effect on cIMT was age (0.312) followed by BP (0.228), Blood glucose control (0.108) and non-HDL (0.134). BMI only had a significant indirect effect through blood glucose control, BP & non-HDL. High sensitivity C-reactive protein (CRP) had a small indirect effect through blood glucose control (all $p = 0.05$).

Conclusions: Age and BP are the major factors with direct effect on cIMT. Glucose and non-HDL were also important in this cohort with a high prevalence of T2DM. BMI only has indirect effects, through other risk factors. Traditional CV risk factors have important direct effects on cIMT in the young, but adiposity exerts its influence only through other CV risk factors.

1. Introduction

Risk-factor related increase in carotid intima-media thickness (cIMT) is associated with cardiovascular (CV) events in adults [1]. Strong evidence links CV risk factors measured in childhood (12 years of age and younger) with increased cIMT in adulthood [2]. Emerging data suggest that carotid thickening occurs as early as adolescence in high risk youth [3]. Which risk factors have the strongest association with cIMT in children and adolescents is less clear, with some studies suggesting blood pressure (BP) [4], others obesity [5], or lipids having the most influence [6]. In this study, we sought to examine the pathways by which risk factors influence cIMT in adolescents and young adults (older than 18 years). Due to the complexity of the relationships between these risk factors, we applied structural equation modeling to estimate biologically plausible pathways through which CV risk factors were associated with increased cIMT. Structural equation modeling (SEM) is an extension of the general linear model taking into account the

Abbreviations: BMI, Body mass index; BP, blood pressure; cIMT, carotid intima-media thickness; CRP, high sensitivity C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high density lipoprotein cholesterol concentration; LDL, Low-density lipoprotein cholesterol concentration; Non-HDL, non-high density lipoprotein cholesterol concentration; SEM, Structural equation modeling; SBP, Systolic blood pressure; T2DM, type 2 diabetes mellitus.

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[1] Indirect association of BMI with Carotid IMT.

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modeling of independent and correlated errors. In SEM, 'latent' variables are derived by modeling groups of measured variables (i.e. 'intelligence' cannot be directly measured but might be inferred from a set of cognitive function tests). This is performed where direct measurement of the variable may be prone to error. SEM adjusts for the error in the latent variable resulting in more unbiased estimates for the relations between all the variables as compared to general linear models. In addition to assessing direct associations between dependent and independent variables, SEM also allows for assessment of mediation and moderation (indirect associations through other factors).

2. Methods

2.1. Population

The population was drawn from the baseline examination of an ongoing longitudinal study. This study was designed to compare and contrast the effects of obesity and type 2 diabetes mellitus (T2DM) on the CV system [3]. All subjects age 10–24 years with T2DM (N = 253) were eligible. Subjects with T2DM were matched by age, race and sex to an obese control (BMI ≥ 95th percentile, N = 256) proven non-diabetic by oral glucose tolerance test, and a lean control (BMI < 85th%, N = 275). Mean age of the cohort was 18.0 ± 3.3 years. The diagnosis of type 2 diabetes was based on the American Diabetes Association criteria [7,8].: the participants had fasting plasma glucose levels ≥ 126 mg/dl or symptoms of hyperglycemia and random plasma glucose ≥ 200 mg/dl, or 2-hr plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test. Written informed consent was obtained from subjects ≥ 18 years old or the parent or guardian for subjects < 18 years old according to Institutional Review Board at Cincinnati Children's Hospital guidelines, in accordance with the Declaration of Helsinki.

2.2. Measurements

Demographics and anthropometric data were collected and fasting blood for glucose, insulin, lipids, high sensitivity C-reactive protein (CRP) and hemoglobin A1c (HbA1c) were drawn after a 10-h overnight fast. The mean of 2 measures of height and weight were obtained with a calibrated stadiometer (Veeder-Rood, Elizabethtown, NC) and an electronic scale (Health-O-Meter, model 770; SECA, Hanover, MD). The mean of 2 measures of blood pressure was obtained with a mercury Sphygmomanometer (W. A. Baum Co., Inc., Copiague, NY) according to the standards of the Fourth Report on Blood Pressure Control in Children [9]. The fifth Korotokoff phase was designated as diastolic BP. Laboratory techniques and reproducibility data have been published previously [3]. Coefficient of variation for repeat measures of SBP were 1.9% and for DBP 4.1%. Assays of fasting plasma lipids (total cholesterol, low-density lipoprotein cholesterol concentration (LDL), high density lipoprotein concentration (HDL) and triglycerides) were carried out in a laboratory that is National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention standardized. LDL was calculated using the Friedewald equation. Non-HDL was calculated as total cholesterol– HDL.

Carotid ultrasound was performed using B-mode ultrasonography with a GE Vivid 7 ultrasound imaging system (GE Medical Systems, Wauwatosa, WI) with a high-resolution linear array transducer with at 7.5 MHz center frequency. The far wall of each carotid segment was examined independently from all angles to identify the thickest cIMT for bilateral common (1 cm proximal to bulb), bulb and internal carotid arteries. Multiple digital image loops were transmitted using the Camtronics Medical System (Hartland, WI) for offline reading which was performed at end diastole. A manual tracing technique was employed to measure the maximum carotid thickness from the leading edge (lumen-intima) to the leading edge (medial-adventitia). Due to the young age of the cohort, few plaques were noted. Readings were not performed at the site of plaque. All images were read by a single experienced and research-trained Registered Vascular Sonographer who was blinded to subject group. The mean cIMT measures of right and left carotid segments were used in analyses. Coefficient of variation for repeat measures of IMT with our more advanced reading techniques were 3.1% for the common and bulb and 3.7% for the internal carotid artery which are improved compared to previous work by our group [3].

2.3. Statistical analysis

SAS 9.3 and SAS Structural Equation Modeling for JMP were used for analyses (SAS Institute Inc., Cary, NC). A two sided $p < 0.05$ was considered significant. Categorical variables were summarized as frequency and percentage. Continuous variables were summarized as mean and standard deviation. The proportion of racial and sex groups were compared using Pearson $\chi 2$ Test. Fasting insulin, glucose, HbA1C, high density lipoprotein cholesterol concentration (HDL), LDL, triglycerides, non-high density lipoprotein cholesterol concentration (non-HDL) and cIMT values were log transformed. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) z-scores were calculated according to the Fourth Report on Blood Pressure Control in Children[9]. Body mass index (BMI) z-score was calculated according to the U.S. Centers for Disease Control and Prevention [10]. Bivariate relationships between CV risk factors and carotid segments were analyzed using Pearson correlation coefficients. Multivariable regression analysis was performed to assess independent determinants of cIMT and age–group interaction. In our previous work[3] we found an age by group interaction such that there was less of an effect of age on cIMT in T2DM. Therefore, we tested for an interaction between age and recruitment group (Lean, Obese, T2DM) in these analyses. We also tested for sex interactions but none were found. The full model included group, age, age–group interaction, sex, race, BMI z-score, SBP z-score, DBP z-score, CRP, fasting lipids, insulin, glucose and HbA1c. The variance inflation factor was < 5 for the model therefore, significant collinearity among SBP and DBP, Glucose and HbA1c, or Group and BMI z-score was not present.

Structural equation models based on previous findings [11,12] and theoretical rationales were tested to examine the relationships among CV risk factors (Fig. 1). Structural equation modeling allows measurement models and latent variables as a feature, where an outcome or factor could not be measured directly but though multiple indicators. We treated the individual segments of cIMT, BP z-scores, glucose and HbA1c as indicator (measured) variables, assuming each of them has measurement errors. Three latent variables or factors (cIMT, blood glucose control, and BP) were extracted from indicator variables to reduce error variances. For example, we can measure common, bulb and internal cIMT and obtain a mean and standard deviation (estimation of error). The SEM technique can then calculate a latent "cIMT" variable and estimate a value that explains more of the variance than explained in any of the 3 individual variables with less error. Latent variable "cIMT" was used to represent the 3 cIMT segments. Latent variable "BP" was extracted from SBP z-score and BP z-score. Latent variable "blood glucose control" was extracted from fasting glucose and HbA1c. Non-HDL was used because it consists of LDL and very low LDL which is part triglycerides. In the model structure, age, race, sex and BMI z-score were always independent variables. All other variables except indicator variables were regressed on age, race, sex and BMI z-score as well as variables lower in the pathway. A path