NONTRADITIONAL CARDIOVASCULAR RISK FACTORS IN PEDIATRIC METABOLIC SYNDROME

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Objective To study the relationships between nontraditional cardiovascular (CV) risk factors and components of the metabolic syndrome in Native Canadian children, a population at risk of future CV disease.

Study design CV risk factors were evaluated in a population-based study of a Canadian Oji-Cree community, involving 236 children aged 10 to 19 years.

Results Using an age- and sex-specific case definition, 18.6% of the children met criteria for pediatric metabolic syndrome. As the number of metabolic syndrome component criteria increased, C-reactive protein, leptin, and ratio of apolipoprotein B to apolipoprotein A1 levels rose (all $P < .0001$) and adiponectin concentration decreased ($P = .0006$). Principal factor analysis using both traditional and nontraditional CV risk factors revealed 5 underlying core traits, defined as follows: adiposity, lipids/adiponectin, inflammation, blood pressure, and glucose.

Conclusions Nontraditional CV risk factors accompany the accrual of traditional risk factors early in the progression to pediatric metabolic syndrome. Furthermore, inclusion of these factors in factor analysis suggests that 5 core traits underlie the early development of an enhanced CV risk factor profile in Native children. *(J Pediatr 2006;148:176-82)*

The metabolic syndrome identifies a patient population at high risk of future development of cardiovascular disease (CVD) and type 2 diabetes (type 2 DM).[1] The risk of atherosclerotic disease in affected patients, however, is not fully reconciled by the cluster of traditional cardiovascular (CV) risk factors that define this syndrome (central obesity, hyperglycemia, hypertension, hypertriglyceridemia, decreased high-density-lipoprotein [HDL] cholesterol).[1] Thus the relationship between the metabolic syndrome and novel nontraditional CV risk factors, including the inflammatory biomarkers C-reactive protein (CRP), serum amyloid A (SAA), and interleukin-6 (IL-6); the adipocyte-derived cytokines adiponectin and leptin; and the ratio of apolipoprotein B to apolipoprotein A1 (apoB:A1) is of interest. These nontraditional CV risk factors have shown independent associations with CVD, after adjustment for traditional risk factors.[2-5] Furthermore, elevated CRP concentration and hypoadiponectinemia, in particular, have both emerged as independent predictors of incident CVD.[2,3]

To study the pathophysiology of CVD, numerous investigators have used the multivariate correlation technique of factor analysis to reduce the cluster of interrelated CV risk factors observed in the metabolic syndrome to a set of discrete underlying core traits.[6] Focusing on traditional CV risk factors, these studies have typically identified a set of 2 to 4 fundamental traits underlying the CV risk factor profile.[6] Importantly, however, the contribution of nontraditional factors in this context has received limited attention to date.

Native North American populations are experiencing high prevalence rates of both traditional and nontraditional CV risk factors, as well as vascular and metabolic

ANOVA	Analysis of variance	HDL	High-density lipoprotein
apoB:A1	Ratio of apolipoprotein B to apolipoprotein A1	HOMA-IR	Homeostasis model assessment index
BMI	Body mass index	IL-6	Interleukin-6
CRP	C-reactive protein	LDL	Low-density lipoprotein
CV	Cardiovascular	NHANES-III	Third National Health and Nutritional Survey
CVD	Cardiovascular disease	SAA	Serum amyloid A
DM	Diabetes mellitus		

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disease.[7-9] Indeed, although overall rates of CVD and associated mortality have been declining in North America, Native populations have exhibited the opposite trend.[9,10] Particularly of concern, with respect to the future, is the growing prevalence of CV risk factors, including obesity and early-onset type 2 diabetes mellitus (DM), in Native children.[11]

Since CV risk factors in childhood track into adulthood and can predict future CVD,[12] evaluation of the metabolic syndrome in Native children offers a potential model for studying early events in the development of vascular disease. While studies of metabolic syndrome in childhood have traditionally been hampered by the lack of a standard definition, de Ferranti et al recently proposed a definition of pediatric metabolic syndrome based on extrapolation from Adult Treatment Panel-III (ATP-III) criteria.[13]

In this report, we evaluate the prevalence of metabolic syndrome in Native Canadian children participating in a population-based study. We hypothesized that nontraditional CV risk factors would be associated with pediatric metabolic syndrome and that inclusion of these variables in factor analysis would provide novel insights into the pathophysiological underpinnings of CVD.

METHODS

The methodology of the Sandy Lake Health and Diabetes Project has previously been described in detail.[7,8,11] In brief, 728 of 1018 eligible residents of Sandy Lake, an Oji-Cree community in northwestern Ontario, participated in a population-based cross-sectional survey to determine the prevalence of type 2 diabetes and associated risk factors. There were 236 participants aged 10 to 19 years, representing participation of 72.6 % of the eligible population in this age range. Signed, informed consent was obtained from all participants or their parents or guardians. The study was approved by the Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee. Interviews and examinations were conducted by trained community members.

Participants underwent oral glucose tolerance testing, with measurement of blood pressure and body anthropometry (height, weight, waist circumference, percentage body fat), as described previously.[7,8,11] Fasting insulin, CRP, IL-6, SAA, adiponectin, leptin, total cholesterol, triglycerides, HDL, and low-density-lipoprotein (LDL) cholesterol were measured as previously described.[7,8,14,15] Apolipoprotein B (apoB) and apolipoprotein A1 (apoA1) were measured using the Behring BN100 nephelometer and Behring reagents.[16] Insulin resistance was estimated using the homeostasis model assessment index (HOMA-IR).[17] Diabetes was diagnosed according to 1985 World Health Organization criteria.[18]

As recently proposed, the definition of metabolic syndrome in children aged 10-19 years was determined based on extrapolation from ATP-III criteria.[13] Pediatric metabolic syndrome was defined by the presence of 3 or more of the following 5 criteria: (1) triglycerides $\geq$1.1 mmol/L; (2) HDL < 1.2 mmol/L in boys aged 15 to 19 years or HDL < 1.3 mmol/L in all other children; (3) fasting blood glucose $\geq$ 6.1 mmol/L; (4) waist circumference $\geq$90th percentile for age and sex; and (5) blood pressure $\geq$ 90th percentile for age, sex, and height. The triglyceride and HDL thresholds were originally derived from pediatric percentiles and have been previously used in the definition of pediatric metabolic syndrome.[13] The hyperglycemia threshold is based on the ATP-III cut point and has also been previously used in the definition of pediatric metabolic syndrome.[13] The 90th percentile of waist circumference for age and sex was determined from the Third National Health and Nutrition Examination Survey (NHANES-III).[19] The 90th percentile of systolic and diastolic blood pressure for age, sex, and height was determined from the recommendations of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.[20] Because waist circumference and blood pressure percentiles were available up to the ages of 17 and 18 years, respectively, the thresholds of the highest available age group were carried forward for older children (18- and 19-year-olds for waist and 19-year-olds for blood pressure). Results were not significantly different if ATP-III criteria for waist and blood pressure were used instead in these older children.

Statistical Analysis

All analyses were conducted using the Statistical Analysis System (SAS 8.02; SAS Institute, Cary, NC). The distributions of continuous variables were assessed for normality, and the natural log transformations of skewed variables (fasting insulin, HOMA-IR, fasting and 2-hr pc blood glucose, CRP, IL-6, SAA, leptin) were used in subsequent analyses. Analysis of variance (ANOVA) and χ^2 tests were used to assess univariate differences between continuous and categorical variables, respectively. Given the potential confounding effect of diabetes, univariate associations between traditional and nontraditional CV risk factors were assessed by Spearman correlation analysis restricted to nondiabetic participants (n = 231). Principal factor analysis was conducted with the FACTOR procedure of SAS. The number of factors to be retained was determined on the basis of scree plot analysis (retaining factors above the break in the curve), the proportion of common variance explained (>5%), and established factor interpretability criteria, described and recommended elsewhere.[21] Oblique (promax) rotation was used to obtain a set of underlying interpretable factors. The resultant factor pattern was interpreted using |factor loadings| $\geq$ 0.3.

RESULTS

Demographic, clinical, and metabolic characteristics of the 236 study participants are shown in Table I. Mean age was 14.9 years (range 10-19), and 61% of participants were female. The vast majority (92.9%) of the children had normal glucose tolerance, whereas 11 participants exhibited impaired glucose tolerance and 5 had diabetes. Fifty-six percent reported a history of smoking cigarettes. Overall, 18.6% of the children met criteria for diagnosis of the metabolic syndrome, and