Independent Metabolic Syndrome Variants Predict New-Onset Coronary Artery Disease

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OBJECTIVE — Any combination of metabolic abnormalities may constitute the metabolic syndrome (MetS), conferring coronary artery disease (CAD) risk, but the independent effect of different combinations on CAD onset remains unknown.

RESEARCH DESIGN AND METHODS — Healthy adult siblings (n = 987) of premature CAD (<60 years) case subjects were followed for 9.8 ± 3.8 years. Baseline MetS variables (insulin sensitivity index, waist circumference, systolic blood pressure, HDL cholesterol, and triglycerides) were recombined into five principal components (PC1–5), and risk factor–adjusted proportional hazards for CAD onset of median-dichotomized PCs were estimated.

RESULTS — The significant hazard ratios were as follows: for PC1 (all abnormalities except blood pressure) 1.66 (P = 0.036), PC2 (high blood pressure levels, high HDL cholesterol) 1.71 (P = 0.016), and PC4 (low HDL cholesterol, high insulin sensitivity, low triglycerides) 2.0 (P = 0.001). Traditionally defined MetS had a hazard ratio of 1.32 (P = 0.18).

CONCLUSIONS — Independent MetS variants identified by PC analysis may explain metabolic mechanisms that increase CAD risk better than the presence of traditional MetS.

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A common approach to examining the metabolic syndrome (MetS) uses a simple count without taking into account the correlation structure of dichotomous metabolic abnormalities including increased blood pressure, high triglyceride levels, low HDL cholesterol levels, abdominal obesity, and impaired glucose control (1). The goal of this study was to define the structure of independent patterns of metabolic syndrome variables and determine their ability to predict new-onset coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS

Population and follow-up

The study was approved by the Johns Hopkins Institutional Review Board. Subjects gave informed consent. The sample included 987 apparently healthy white and African American siblings (<60 years) of index case subjects (each identifying 1 of 522 families) admitted to hospitals with CAD events at <60 years of age. New-onset CAD events were followed up over a mean period of 9.8 ± 3.8 years (mean ± SD). Details regarding index case subjects and follow-up adjudication are included in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-2211/DC1.

Screening and metabolic measures

Detailed measurement techniques for blood pressure, fasting lipid profile, glucose, and insulin are included in the online appendix. In addition to variables used by the National Cholesterol Education Program (NCEP)–Adult Treatment Panel (ATP)-III (1)—namely systolic blood pressure, fasting triglycerides and HDL cholesterol, and waist circumference—we included the Quantitative Check Index of Insulin Sensitivity {QUICKI = 1/[log(fasting insulin) + log(fasting glucose)]} (2) because other definitions of MetS (3,4) include insulin resistance.

Statistical analysis

Principal component (PC) calculation adjusting for age, sex, and family structure and their interpretation are detailed in the online appendix. PC variants were dichotomized at the median score. Cox proportional hazard models were evaluated with age of CAD onset as the underlying time scale, adjusting for sex, race, current smoking, LDL cholesterol, and blood pressure medication use. A regression model for NCEP–ATP-III MetS (as defined by Grundy et al. [1]) was also estimated.

RESULTS

Sample characteristics

The sample of 987 individuals consisted of 40% male and 58% African American and had an age range of 27–60 years. Table A1 (available in the online appendix) shows baseline sample characteristics by new-onset CAD event status during follow-up (106 events in 99 families).

Principal components analysis of metabolic variables

Table A2 shows the proportion of variance in the metabolic variables explained by the five PC-derived components and their eigenvector weights. Nearly half (49%) of the variance is explained by the first principal component (PC1), which represents quantitatively greater waist and triglycerides and lower HDL cholesterol and insulin sensitivity when positive and the converse when negative. PC1 values strongly correlate with the prevalence of NCEP-defined MetS (highest PC1 quartile: 92%, lowest PC1 quartile: 2%, NCEP-MetS prevalence, trend P <

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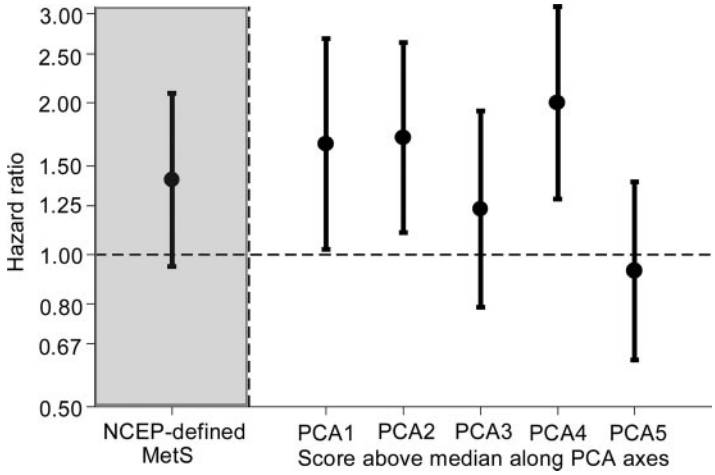

Figure 1—*Hazard ratios for CAD and 95% CIs for baseline metabolic status for the NCEP-defined metabolic syndrome (MetS present vs. MetS absent) in one model and all five PCA scores dichotomized at the median (score > median vs. ≤ median) in the other model. Models adjusted for age, sex, race, smoking, total cholesterol, and blood pressure medication use.*

0.001). Positive scores for other PC axes represent the following: PC2, high systolic blood pressure and high HDL cholesterol; PC3, low waist circumference and high QUICKI with high systolic blood pressure and triglycerides; PC4, high QUICKI and low triglycerides but with low HDL cholesterol; PC5, high QUICKI, large waist circumference, and high triglycerides; negative scores represent opposite patterns.

Association of MetS principal components with new-onset CAD

Unadjusted incidence curves by PC score are shown in Fig. A1 in the online appendix. The age, sex, race, and risk factor–adjusted relative hazards of the PCs (dichotomized at the median) and NCEP–ATP-III MetS are shown in Fig. 1. PC1, PC2, and PC4 are independently associated with a significant hazard ratio of new-onset CAD. The hazard ratio associated with the higher level of PC1 is greater than that associated with the NCEP-defined MetS (estimated in a separate model), which is not statistically significant in this sample.

CONCLUSIONS — This is the first study demonstrating the association of PC-derived independent metabolic syndrome variants with new-onset CAD events in an initially healthy population. PC4 representing lower HDL cholesterol levels in the absence of insulin insensitivity and other metabolic variables doubles the risk of CAD. PC1, although it resembles the ATP-III–defined MetS (1), produces a much more potent estimate of risk for incident CAD than the ATP-III–defined MetS, because it weights the metabolic abnormalities better than a simple count. Furthermore, the linear PC combination threshold at the mean may be more efficient than the predefined traditional thresholds. PC2 representing mostly higher systolic blood pressure in an otherwise healthy metabolic context causes a 70% increase in the risk of incident CAD. In addition, the PC analysis also shows that higher triglyceride levels as found in PC3 and PC5 are not associated with incident CAD unless they occur in the presence of multiple other metabolic risk factors, as in PC1. Importantly, these CAD-related PC variants are not captured in the NCEP–ATP-III MetS.

Although PC4 represents only 9% of the metabolic variation, it is significantly associated with incident CAD independently of the other variables and PC variables. This component (insulin sensitivity combined with lower HDL cholesterol and lower triglycerides) would be ignored by previous PC analyses (5,6) where dimensionality reduction, rather than defining CAD risk, was the primary intent.

Systemic manifestations of insulin resistance underpin for the pattern of correlation represented by our PC1 (7). Superimposed on PC1, HDL cholesterol levels are associated with differential risk based on the pattern of other metabolic variables. We may speculate that lipid dysmetabolism including more atherogenic subfractions of HDL may manifest as PC2 (8). However, unifying biological themes may underlie the other PC variables and remain to be discovered.

Strengths and limitations

The prospective design allowing analysis of the age of CAD onset in an easily identifiable white and African American high-risk cohort is a significant strength. Further replication in the general population would make the study results more widely applicable. A limitation of PC analysis is that the choice of variables can be somewhat arbitrary. However, variables we chose include important features of most current MetS definitions.

In conclusion, we have shown that independent of the well-known MetS pattern, and superimposed upon it, there is significant risk of CAD conferred by two other novel metabolic patterns: high blood pressure with high HDL cholesterol and high insulin sensitivity with low HDL cholesterol and low triglycerides. Further basic and clinical research is needed to elucidate the biological underpinnings of our results.

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No potential conflicts of interest relevant to this article were reported.

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