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The Relationship of Insulin Resistance and Extracoronary Calcification in the Multi-Ethnic Study of Atherosclerosis

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Abstract

OBJECTIVE—We hypothesized that insulin resistance, measured by the homeostatic model assessment of insulin resistance (HOMA), is independently associated with prevalent and incident extra-coronary calcification (ECC).

METHODS—We studied calcium scores of the aortic valve (AVC), mitral valve (MVC), thoracic aorta (TAC) and aortic valve root (AVR) in 6,104 MESA participants not on diabetes medication who had baseline cardiac CT scans; 5,312 had follow-up scans (mean 2.4y). Relative-risk

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regression modeled prevalent and incident ECC adjusted for baseline demographics (model 1), and additionally for CVD risk factors (model 2).

RESULTS—In model 1, prevalence and incidence risk-ratios for the highest versus lowest quartile of HOMA were 20–30% higher in all ECC locations (p-value for trend ≤ 0.05 for all but incident-AVC). In model 2, all associations were attenuated, primarily by adjustment for metabolic syndrome components.

CONCLUSIONS—HOMA has a positive and graded association with ECC, but not independently of cardiovascular risk factors—particularly metabolic syndrome components.

Keywords

cardiovascular calcification; insulin resistance; atherosclerosis; metabolic syndrome; computed tomography; valvular calcification; thoracic aortic calcification

1. INTRODUCTION

Insulin resistant states, including the metabolic syndrome and overt diabetes, have been strongly associated with subclinical and clinical cardiovascular disease (CVD) and all-cause mortality [1, 2]. There is increasing evidence that calcification in coronary and extra-coronary locations may reflect a generalized process of atherosclerosis [3, 4]. Indeed, many processes and risk factors underlying cardiovascular calcification, including inflammation, oxidative stress, dyslipidemia and endothelial dysfunction, are systemic metabolic insults which are additionally associated with the “pro-atherogenic” milieu of insulin resistance [5].

The sequelae of resistance to insulin-mediated glucose uptake is widespread, with one cluster of risk factors known as the “metabolic syndrome” lying downstream in the causal pathway for cardiovascular disease [5]. Whether insulin resistance influences cardiovascular calcification beyond the metabolic syndrome components and traditional CVD risk factors is unclear. Studies exploring the independent association of insulin resistance with coronary artery calcification have yielded mixed results [6, 7]. Few studies have examined the relationship of insulin resistance on other measures of subclinical atherosclerosis. We aimed to study the association of insulin resistance with several measures of extracoronary calcification (ECC), and hypothesized that insulin resistance is independently associated with prevalent and incident ECC.

2. METHODS

MESA enrolled 6,814 men and women aged 45–84 years, free of clinical CVD at baseline, recruited from six US centers [8]. For prevalence analyses, we excluded participants receiving treatment for diabetes (n=680), and those with no baseline assessment of insulin resistance (n=30) for a study population of 6,104; for incidence analyses, we additionally excluded those with no follow-up CT scan data (n=792) for a study population of 5,312. For incidence analysis of ECC, those with baseline prevalent ECC for that measure were excluded.

The primary predictor variable for this analysis is the Homeostasis Model of Insulin Resistance (HOMA) which was calculated as $\{[\text{fasting insulin (mU/L)} \times \text{fasting glucose (mg/dl)}] / 405\}$ [9]. Total and high density lipoprotein (HDL) cholesterol, glucose and insulin were measured after a 12 hour fast. Metabolic syndrome was defined using the National Cholesterol Education Panel, Adult Treatment Panel III definition. Quartiles of HOMA were calculated for regression analyses. Cardiac CT was performed at 3 sites using the Imatron C-150XL scanner (GE-Imatron, San Francisco, California), and 3 sites used 4-slice

multidetector scanners. Baseline scans were performed twice on all participants, with scores averaged. A second scan was obtained on a random selection of half the cohort at exam 2, and the other half at exam 3, (total mean time between scans was 2.4 years $\pm$ 0.9 years). The outcome variables in this study were the four ECC measures, determined by CT scan: aortic valve calcification (AVC), mitral valve calcification (MVC), thoracic aorta calcification (TAC) and aortic valve root calcification (AVR). All ECC measures were scored using the Agatston method; single lesion measurements were summed to give an overall Agatston score. Methods of ECC measurement have been previously described [10]. The absence of AVC, MVC, TAC or AVR was assigned a score of zero.

Risk ratio (relative risk) regression was preferred over logistic regression since the prevalence of ECC measures in our study was $>10\%$, making the odds ratio likely to overestimate the risk ratio. Estimates of the prevalence ratio and risk (incidence) ratio for ECC were calculated separately from the regression model $y = \exp(X^T\beta)$. The exponentiated parameter β is interpreted as the prevalence or risk ratio. We assumed Gaussian error and used robust standard error estimates. Two hierarchical regression models were utilized. Model 1 was adjusted for basic demographic variables, which included baseline age (continuous), gender, ethnicity (Caucasian, Chinese, African American, Hispanic) and MESA study site. Model 2 was adjusted for other CVD risk factors in addition to model 1 covariates, including hypertension, smoking status (never, former, current), use of cholesterol lowering medication, low density lipoprotein-cholesterol (LDL), high density lipoprotein-cholesterol (HDL-C), high-sensitivity C-reactive protein, education ($\geq$ high school, $<$ high school), family history of myocardial infarction and body mass index. All incidence analyses (risk ratios) were additionally adjusted for time between CT scans to account for follow-up duration. Individuals missing relevant covariates were excluded from regression analysis. Interactions were examined with age, gender, ethnicity and hypertension; no statistically significant interactions were found at $\alpha \leq 0.05$. C-reactive protein was skewed and was natural-log-transformed. All analyses were performed using STATA 10.0 (Stata Co., College Station, TX).

3. RESULTS

Table 1 shows the baseline characteristics of the study participants by HOMA quartile. In models adjusted for basic demographics (model 1), positive associations were observed between increasing HOMA quartile and prevalent ECC (Table 2). The MVC p-value for trend across HOMA quartiles was borderline, though the individual p-value for the highest versus the lowest quartile of HOMA was significant at $p=0.03$. Upon additional adjustment for CVD risk factors (model 2), HOMA was no longer significantly associated with prevalent ECC at any location. The covariates of BMI and HDL were responsible for the greatest degree of attenuation of the ECC prevalence ratios.

Upon basic adjustment (model 1), higher HOMA quartiles demonstrated a positive and graded association with incident ECC for all measures (Table 2). The incident AVC p-value for trend was not significant. Upon additional adjustment (model 2), associations were attenuated and statistical significance was lost for all ECC measures. Similar to prevalence analyses, BMI, HDL and additionally hypertension were the covariates that caused the greatest degree of attenuation of the ECC risk ratios.

Sensitivity analyses using a dichotomous variable denoting the metabolic syndrome and also with and without adjustment for metabolic syndrome components corroborated our finding that the metabolic syndrome components were most responsible for attenuating the association of insulin resistance and ECC. We re-fit all models with quartiles of log-transformed HOMA, as this has been suggested to correlate more strongly with glucose

clamp across wide ranges of insulin sensitivity, including insulin resistance, glucose intolerance and moderate diabetes [11]. Point estimates and statistical significance were essentially unchanged. In addition, we adjusted for estimated glomerular filtration rate (mL/min/1.73 m²) and excluded those with untreated diabetes from our population (n=178), which only minimally altered results.

4. DISCUSSION

We demonstrate that after adjustment for age, sex and ethnicity, HOMA has a positive and graded association with the presence and development of ECC at most locations. This association was not independent of CVD risk factors, however, and the metabolic syndrome components play a predominant role in mediating this association.

In the causal pathway of CVD development, insulin resistance is thought to be an early insult with various downstream mediators including inflammation, oxidative stress, dyslipidemia and endothelial dysfunction [5]. Cardiovascular calcification is an actively regulated process similar to bone formation, and histopathologic and molecular similarities have been demonstrated between vascular atherosclerotic calcification and valvular calcification [4, 12]. The systemic inflammatory milieu characteristic of insulin resistant states promotes many of these pro-calcific mechanisms, raising the question of whether the upstream entity of insulin resistance may play an independent role in a generalized atherosclerotic process.

Studies examining this association using carotid artery intima medial thickness or CAC have shown mixed results [1, 7, 13]. One recent study did report, however, a positive association between fasting insulin and angiographically determined coronary atherosclerotic disease severity [14], which may not be appreciated using CAC alone. Katz et al. recently reported a positive association of increasing numbers of metabolic syndrome components with both prevalent and incident AVC, also using the MESA cohort [15].

Our study is unique in assessing calcification at various extra-coronary sites within the same population and does not show HOMA to be independently associated with the development of calcification at any of these sites. HOMA provides an estimate of insulin resistance which, though not identical to the “gold standard” of the hyperinsulinemic-euglycemic clamp, is generally well correlated with this measure and can be most useful when estimating broad categories of insulin resistance within large-population epidemiologic studies such as ours [9, 11].

One of the more important findings from this study is that metabolic syndrome components were responsible for the greatest degree of attenuation of the initial association seen between HOMA and ECC. Thus, while insulin resistance lies causally upstream with various possible pleiotropic effects, our findings suggest that the well-described downstream cluster of metabolic syndrome components is likely to mediate the majority of its influence on vascular calcification in several locations. Furthermore, it suggests that the adequate treatment of hypertension, dyslipidemia and obesity in patients with insulin resistance states may significantly decrease the clinical sequelae of insulin resistance such as cardiovascular calcification.

Limitations of our study include the loss of participants to follow-up between serial CT scans (n=792) and the possibility that the duration of time between CT scans may not have been adequate to demonstrate an association of insulin resistance with ECC. In addition, our use of HOMA only estimates more direct measures of insulin resistance, such as the hyperinsulinemic euglycemic clamp, which were not available in MESA.

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Table 1
 Characteristics between quartiles of HOMA in the Multi-Ethnic Study of Atherosclerosis (2000–2002)

Variable	HOMA Q1 (n=1,526)	HOMA Q2 (n=1,527)	HOMA Q3 (n=1,525)	HOMA Q4 (n=1,526)	p-value
Male %	44.4	45.2	48.2	49.5	0.01
Age (year)	62.0 SD(10.6)	62.0 SD(10.3)	62.8 SD(10.5)	61.4 SD(9.7)	<0.01
Ethnicity % (row)					
Caucasian	32.5	25.4	23.0	19.1	<0.01
Chinese	22.3	31.3	26.2	20.2	
African American	22.1	23.1	25.7	29.2	
Hispanic	15.6	23.1	27.3	34.1	
Body Mass Index (kg/m ²)	24.6 SD(3.9)	26.9 SD(4.3)	29.1 SD(4.9)	31.8 SD(5.4)	<0.01
Waist Circumference (cm)	87.7 SD(11.1)	94.3 SD(11.4)	100.4 SD(12.5)	107.1 SD(13.3)	<0.01
Waist to Hip Ratio	0.88 SD(0.08)	0.91 SD(0.07)	0.94 SD(0.07)	0.96 SD(0.07)	<0.01
Diabetes Mellitus [†] %					
Normal	97.5	93.6	82.7	59.2	<0.01
Impaired Fasting Glucose	2.4	5.6	15.3	32.0	
Untreated Diabetes	0.1	0.8	2.0	8.8	
Smoking % (column)					
Never	48.2	51.8	51.5	49.9	0.21
Former	38.3	34.5	35.8	38.0	
Current	13.6	13.6	12.7	12.1	
Education (>High School) %	88.3	84.1	81.5	78.6	<0.01
Family History of MI (yes) %	41.3	38.2	39.7	41.4	0.19
Hypertension [‡] % (column)					
Normal	54.1	49.2	42.0	32.5	<0.01
Prehypertension	26.0	29.4	33.1	37.6	
Hypertension Stage 1	14.8	15.8	17.4	20.3	
Hypertension Stage 2	5.2	5.6	7.6	9.6	
Systolic blood pressure (mmHg)	121.5 SD(21.9)	124.0 SD(21.0)	127.0 SD(20.8)	131.0 SD(20.2)	0.02
Estimated Glomerular Filtration Rate (mL/min/1.73 m ²)	80.4 SD (19.3)	79.8 SD(16.2)	80.9 SD(16.6)	82.0 SD(18.3)	<0.01
Total Cholesterol (mg/dl)	193.3 SD(32.6)	196.0 SD(35.0)	196.5 SD(35.8)	194.8 SD(37.2)	<0.01

Variable	HOMA Q1 (n=1,526)	HOMA Q2 (n=1,527)	HOMA Q3 (n=1,525)	HOMA Q4 (n=1,526)	p-value
LDL Cholesterol (mg/dl)	115.2 SD(30.2)	118.5 SD(30.4)	120.2 SD(31.4)	118.4 SD(31.8)	0.13
HDL Cholesterol (mg/dl)	59.0 SD(16.6)	53.6 SD(14.4)	48.5 SD(12.9)	44.9 SD(11.4)	<0.01
C-Reactive Protein (mg/L)	2.8 SD(5.8)	3.5 SD(6.2)	3.8 SD(5.0)	4.8 SD(5.9)	<0.01
Anti-HTN meds % (yes)	24.4	29.2	36.3	44.1	<0.01
Lipid lower meds % (yes)	10.2	14.5	14.8	18.6	<0.01

[†] (2003 ADA criteria): Normal if fasting glucose is < 100 mg/dL and not taking diabetes medication; impaired fasting glucose if fasting glucose =100–125 mg/dL and not taking diabetes medications; untreated diabetes if fasting glucose ≥ 126 mg/dL and not taking diabetes medication; treated diabetes if reports taking diabetes medication.

[‡] (JNC VII Guidelines): Normal BP (in mmHg): SBP <120 and DBP <80; Prehypertension BP: SBP 120–139 or DBP 80–89; Stage 1 Hypertension BP: SBP 140–159 or DBP 90–99; Stage 2 Hypertension BP: SBP ≥ 160 or DBP ≥ 100.

Table 2

Adjusted Prevalence and Risk Ratios of Extra-coronary Calcification by HOMA Quartile in the Multi-Ethnic Study of Atherosclerosis (2000–2006)

Model 1 [†]	Aortic Valve Calcium		Mitral Valve Calcium		Thoracic Aortic Calcium		Aortic Valve Root Calcium	
HOMA Quartile	Prevalence Ratio (95% CI)	Risk Ratio (95% CI)	Prevalence Ratio (95% CI)	Risk Ratio (95% CI)	Prevalence Ratio (95% CI)	Risk Ratio (95% CI)	Prevalence Ratio (95% CI)	Risk Ratio (95% CI)
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	1.27 (1.04–1.54)	1.11 (0.58–2.11)	1.13 (0.89–1.45)	1.51 (0.91–2.45)	1.08 (0.99–1.18)	0.83 (0.62–1.09)	1.16 (1.06–1.26)	1.05 (0.80–1.37)
Quartile 3	1.24 (1.02–1.51)	1.25 (0.63–2.46)	1.11 (0.88–1.41)	1.36 (0.78–2.36)	1.02 (0.94–1.12)	1.08 (0.84–1.39)	1.10 (1.00–1.20)	1.17 (0.91–1.52)
Quartile 4	1.36 (1.11–1.66)	1.33 (0.78–2.28)	1.30 (1.02–1.65)	1.78 (1.09–2.92)	1.20 (1.10–1.31)	1.23 (0.96–1.58)	1.20 (1.10–1.31)	1.32 (1.03–1.70)
p-value for trend	<0.01	0.25	0.05	0.04	<0.01	0.05	<0.01	0.02
Model 2 [‡]								
Quartile 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	1.19 (0.97–1.46)	0.86 (0.36–2.07)	1.08 (0.83–1.40)	1.40 (0.63–3.11)	1.04 (0.95–1.13)	0.83 (0.62–1.11)	1.08 (0.99–1.18)	0.91 (0.69–1.21)
Quartile 3	1.14 (0.93–1.41)	0.87 (0.40–1.88)	1.03 (0.80–1.31)	1.11 (0.42–2.96)	0.93 (0.85–1.02)	0.96 (0.70–1.31)	0.98 (0.90–1.08)	0.88 (0.66–1.18)
Quartile 4	1.18 (0.94–1.49)	1.10 (0.50–2.40)	1.17 (0.89–1.53)	1.86 (0.65–5.30)	1.07 (0.97–1.19)	1.07 (0.76–1.50)	1.02 (0.93–1.13)	0.97 (0.73–1.30)
p-value for trend	0.25	0.74	0.38	0.44	0.69	0.57	0.81	0.91

* All prevalence and risk ratios are calculated with HOMA quartile 1 as the referent category.

[†]Model 1 = Adjusted for: baseline age (continuous), gender, ethnicity (Caucasian, Chinese, African American, Hispanic), MESA study site. Incidence analyses (risk ratios) are additionally adjusted for time between CT scans.[‡]Model 2 = model 1 + hypertension, smoking status (never, former, current), use of cholesterol lowering medication, low density lipoprotein-cholesterol (LDL), high density lipoprotein-cholesterol (HDL) high-sensitivity C-reactive protein, education (>high school, <high school), family history of MI and BMI.