

# The Relationship Between Insulin Resistance and Incidence and Progression of Coronary Artery Calcification

The Multi-Ethnic Study of Atherosclerosis (MESA)

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**OBJECTIVE**—We sought to determine whether insulin resistance predicts the incidence and progression of coronary artery calcification (CAC).

**RESEARCH DESIGN AND METHODS**—We studied 5,464 participants not on hypoglycemic therapy from the Multi-Ethnic Study of Atherosclerosis (MESA). Each had baseline homeostasis model assessment of insulin resistance (HOMA-IR) and baseline and follow-up CAC scores. Incident CAC was defined as newly detectable CAC; progression was defined as advancing CAC volume score at follow-up.

**RESULTS**—Median HOMA-IR was 1.2 (0.8–2.0). Across all ethnicities, there was a graded increase in CAC incidence and progression with increasing HOMA-IR. When compared with those in the 1st quartile, participants in the 2nd–4th quartiles had 1.2, 1.5, and 1.8 times greater risk of developing CAC. Median annualized CAC score progression was 8, 14, and 17 higher, respectively. However, HOMA-IR was not predictive after adjustment for metabolic syndrome components.

**CONCLUSIONS**—HOMA-IR predicts CAC incidence and progression, but not independently of metabolic syndrome.

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Sensitivity to insulin-mediated glucose uptake varies at least sixfold in the general healthy population, with variability attributable to genetic and behavioral factors (1–4). In the clinical setting, insulin resistance is commonly inferred via its adverse consequences,

which include dysglycemia, hypertension, low HDL cholesterol (HDL-C), high triglycerides, and subclinical inflammation (collectively, the metabolic syndrome) (5).

Insulin resistance and the metabolic syndrome have both been shown to be

strongly associated with measures of subclinical atherosclerosis, including coronary artery calcification (CAC) (6,7). Consistent with these observations, prospective studies have demonstrated that insulin resistance and metabolic syndrome are independent predictors of cardiovascular events (8,9). However, the degree to which insulin resistance and metabolic syndrome are mutually independent predictors remains debated, with prior results mixed (7,10). We sought to determine whether insulin resistance prospectively predicts the onset and progression of CAC, independent of metabolic syndrome.

## RESEARCH DESIGN AND METHODS

The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled 6,814 men and women of four ethnicities (white, Chinese, African American, and Hispanic) into a population-based study aimed at describing the prevalence, progression, and significance of subclinical atherosclerosis (11). Patients were aged 45–84 without known cardiovascular disease. We excluded participants with no baseline assessment of insulin resistance ( $N = 32$ ) and no follow-up CAC scans ( $N = 768$ ) and/or who were treated with hypoglycemic therapy ( $N = 678$ ), for a final population of 5,464 participants (2,284 whites; 638 Chinese; 1,411 African Americans; and 1,131 Hispanics).

Baseline insulin resistance was defined as homeostasis model assessment of insulin resistance (HOMA-IR), calculated as fasting insulin [ $\mu\text{U}/\text{mL}$ ]  $\times$  fasting glucose [ $\text{mg}/\text{dL}$ ]/405 (MESA 2000–2002). Serum glucose was measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics) and insulin by radioimmunoassay using the Linco Human Insulin Specific RIA kit (Linco Research). Metabolic syndrome was identified using the modified NCEP ATPIII definition.

Baseline cardiac computed tomography was performed twice on all participants,

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with CAC scores averaged. A second CAC measurement was performed on one-half of the cohort at exam 2, and the other half at exam 3, an average of 1.6 and 3.2 years after baseline (MESA 2002–2005). CAC incidence was defined as any detectable CAC in individuals without CAC at baseline. CAC progression was defined as advancing CAC volume score in participants with detectable baseline CAC.

In separate models, we assessed the multivariable-adjusted relationship of HOMA-IR (quartiles and continuous) with CAC incidence and CAC progression. For CAC incidence, we calculated relative risks using a generalized estimating equation with log link and binomial distribution. For CAC progression, we calculated  $\beta$ -coefficients (units = change in CAC volume score/year) using robust linear regression.

**RESULTS**—The mean age of the population was  $62 \pm 10$ , and 53% were women. Median HOMA-IR was 1.2 (0.8–2.0). There was a graded association between increasing HOMA-IR and male sex, African American and Hispanic ethnicity, BMI, untreated diabetes, HDL-C, and triglycerides (all  $P < 0.01$ ). At baseline, 47% of patients had CAC, with a mean volume score of 230 and median volume score of 76 (22–252).

There was a graded association between HOMA-IR quartile and CAC incidence. The rate of incident CAC for the 1st through 4th quartiles was 4.4, 5.4, 6.8, and 7.8 per 100 person-years. Adjusted for age, sex, ethnicity, MESA site, and years in between scans, participants in the 2nd–4th quartiles were 1.2, 1.5, and 1.8 times more likely to develop CAC compared with those in the 1st quartile. Strong associations persisted for all but Hispanics. However, HOMA-IR was no longer predictive after adjusting for metabolic syndrome components and other established risk factors (Table 1).

There was also a graded association between HOMA-IR quartile and CAC progression. Median annualized CAC volume score progression for the 1st through the 4th quartiles was 37, 45, 51, and 55 per year. When compared with the 1st quartile, incremental median annualized CAC score progression was 8, 14, and 17 higher, respectively. In models adjusted for age, sex, ethnicity, MESA site, years in between scans, and log (baseline CAC), there were significantly increased CAC progression rates for the 3rd ( $\beta = 9.4$ , 95% CI 2.2–16.6) and 4th

**Table 1—HOMA quartile (4th vs. 1st) for the prediction of CAC incidence and progression in MESA**

	HOMA 4th quartile vs. HOMA 1st quartile	
	Incident CAC Relative risk (95% CI)	CAC progression† ΔCAC score (95% CI)
Total population		
Model 1	1.78 (1.43–2.22)**	11.5 (4.5–18.4)**
Model 2	1.21 (0.92–1.61)	−3.0 (−11.8 to 5.8)
Model 3	1.02 (0.77–1.35)	−0.9 (−10.2 to 8.5)
White		
Model 1	1.62 (1.15–2.28)**	13.6 (1.3–26.0)*
Model 2	1.03 (0.66–1.60)	−8.3 (−24.2 to 7.6)
Model 3	0.86 (0.57–1.29)	−1.2 (−18.2 to 15.9)
Chinese		
Model 1	3.24 (1.18–8.90)*	8.4 (−6.6 to 23.5)
Model 2	2.98 (0.35–25.7)	2.3 (−22.0 to 12.7)
Model 3	2.49 (0.34–18.4)	−1.4 (−21.9 to 19.0)
African American		
Model 1	1.81 (1.19–2.75)*	9.5 (−4.7 to 23.6)
Model 2	1.08 (0.59–1.98)	−4.7 (−18.2 to 14.5)
Model 3	0.92 (0.50–1.72)	−2.1 (−20.8 to 16.6)
Hispanic		
Model 1	1.51 (0.86–2.65)	7.7 (−6.4 to 21.7)
Model 2	1.32 (0.64–2.74)	−1.5 (−19.0 to 16.1)
Model 3	0.93 (0.44–2.00)	−4.8 (−23.6 to 14.0)

HOMA quartiles: 1st quartile (0.14–0.79), 2nd quartile (0.80–1.24), 3rd quartile (1.24–2.03), 4th quartile (>2.03). Model 1, adjusted for age, sex, ethnicity, MESA site, and years between CAC scans; Model 2, Model 1 + NCEP ATP III metabolic syndrome components (waist circumference, impaired fasting glucose, low HDL-C, high triglycerides, and hypertension [categorical]); and Model 3, Model 1 + NCEP ATP III metabolic syndrome components (continuous) except for impaired fasting glucose (categorical), diabetes, smoking, LDL-C, family history of coronary heart disease, and cholesterol-lowering medications. †Additionally adjusted for log (baseline CAC) in the CAC progression model. \* $P < 0.05$ ; \*\* $P < 0.005$ .

( $\beta = 11.5$ , 95% CI 4.5–18.4) quartiles compared with the 1st quartile. This association was the strongest among whites. However, there was no association after adjusting for metabolic syndrome components or established risk factors (Table 1).

As a continuous variable, HOMA-IR predicted CAC incidence and progression but was not predictive after adjustment for metabolic syndrome components. Each individual component, except for low HDL-C, predicted CAC incidence and progression. HOMA-IR remained predictive in models adjusting for individual components, without evidence of interaction. Normal weight/insulin resistant and obese/insulin sensitive individuals had similar risk of incident CAC; the joint risk with both obesity and insulin resistance was merely additive, without interaction. The results of this study were not changed when participants with untreated diabetes were excluded.

**CONCLUSIONS**—We demonstrate that insulin resistance measured by

HOMA-IR predicts CAC incidence and progression, which are established predictors of adverse events (12), but not independently of metabolic syndrome components. This suggests that although insulin resistance is an important pathobiologic contributor to coronary artery disease, it does not add additional predictive value beyond routine risk assessment.

Mechanistically, insulin resistance lies upstream of the metabolic syndrome and its consequences on the causal pathway for cardiovascular disease. Thus it is less surprising that the predictive value of HOMA-IR is attenuated after multivariable adjustment. Indeed, the metabolic syndrome and its components are independently associated with subclinical atherosclerosis and adverse cardiovascular outcomes (6–9). Recently microalbuminuria, which has been viewed as both a consequence or a defining feature of metabolic syndrome (13), has been shown to predict CAC progression (14). Although debated (8,10), our study argues against routine clinical measurement of HOMA-IR but supports identification of the

metabolic syndrome and measurement of its component risk factors.

Our study adds to a prior study by Lee et al. (15) that demonstrated an independent association between fasting insulin, but not HOMA-IR, and CAC progression. This smaller study (869 patients) of an older (mean age 66 years), more homogeneous population had several limitations. First, the study was likely underpowered. Second, this study examined progression of CAC score and did not separately model incident CAC. Finally, plasma insulin values were used, which are notoriously variable and of limited use when not accounting for plasma glucose (as in HOMA-IR).

In conclusion, insulin resistance predicts CAC incidence and progression in all four ethnicities. However, clinical identification of the metabolic syndrome and measurement of its associated risk factors is preferred over HOMA-IR for predicting coronary atherosclerosis.

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