Title

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Journal

Diabetes Care, 34(3)

ISSN

1066-9442

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Publication Date

2011-03-01

DOI

10.2337/dc10-1681

Peer reviewed

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.

Diabetes Care 34:749–751, 2011

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 [μU/mL] × fasting glucose [mg/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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Received 2 September 2010 and accepted 31 October 2010.
DOI: 10.2337/dc10-1681
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-1681/-/DC1.

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 β-coefficients (units = change in CAC volume score/year) using robust linear regression.

RESULTS—The mean age of the population was 62 ± 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 (β = 9.4, 95% CI 2.2–16.6) and 4th (β = 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).

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 ATPIII metabolic syndrome components (waist circumference, impaired fasting glucose, low HDL-C, high triglycerides, and hypertension [categorical]); and Model 3, Model 1 + NCEP ATPII 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. *$P < 0.05$; **$P < 0.005$.

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 homogenous 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.

Acknowledgments—This research was supported by the National Institutes of Health National Heart, Lung, and Blood Institute (Grant R01-HL-071739 and contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169).

M.J. Budoff is on the speaker's bureau for General Electric and runs the CT reading center for MESA. No other potential conflicts of interest relevant to this article were reported.

M.J. Blaha was involved in all steps of this study/article. A.P.D., J.J.R., M.J. Budoff, R.B., A.A., M.S., S.G.L., A.G.B., R.A.K., and R.S.B. were involved in study planning, data interpretation, abstract editing, and article editing. K.N. was involved in all steps of this study/article.

The authors thank the other investigators, the staff, and the participants of the MESA study for valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

References

1. Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. Diabetes Care 2000; 23:171–175
2. Ho LT, Chang ZY, Wang JT, et al. Insulin insensitivity in offspring of parents with type 2 diabetes mellitus. Diabet Med 1990;7:31–34
3. Nassis GP, Papantakou K, Skenderi K, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. Metabolism 2005;54:1472–1479
4. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven GM. Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol 1985; 248:E286–E291
5. Blaha MJ, Bansal S, Rouf R, Golden SH, Blumenthal RS, Defilippis AP. A practical "ABCDE" approach to the metabolic syndrome. Mayo Clin Proc 2008;83:932–941
6. Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. J Am Coll Cardiol 2003;41:1547–1553
7. Bertoni AG, Wong ND, Shea S, et al. Insulin resistance, metabolic syndrome, and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2007;30:2951–2956
8. Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. Diabetes Care 2010;33:1179–1185
9. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49:403–414
10. Reilly MP, Wolfe ML, Rhodes T, Girman C, Mehta N, Rader DJ. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. Circulation 2004;110:803–809
11. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002; 156:871–881
12. McEvoy JW, Blaha MJ, Defilippis AP, et al. Coronary artery calcium progression–an important clinical measurement? A review of published reports. J Am Coll Cardiol 2010;56:1613–1622
13. Blaha MJ, Elasy TA. Clinical use of the metabolic syndrome: why the confusion? Clin Diabetes 2006;24:125–131
14. DeFilippis AP, Kramer HJ, Katz R, et al. Association between coronary artery calcification progression and microalbuminuria: the MESA study. JACC Cardiovasc Imaging 2010;3:595–604
15. Lee KK, Fortmann SP, Fair JM, et al. Insulin resistance independently predicts the progression of coronary artery calcification. Am Heart J 2009;157:939–945