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Usefulness of Insulin Resistance Estimation and the Metabolic Syndrome in Predicting Coronary Atherosclerosis in Type 2 Diabetes Mellitus

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Abstract

Metabolic syndrome (MS) definitions predict cardiovascular events beyond traditional risk factors in type 2 diabetic (DM) as well as non-diabetics subjects. We and other have shown that apolipoprotein B (apoB) and non-HDL cholesterol (non-HDL-C) are associated with coronary artery calcification (CAC) in DM. However, the relative value of MS, apoB lipoproteins and estimates of insulin resistance is unknown in predicting atherosclerosis in DM. We performed cross sectional analyses of white subjects in 2 community based studies (N= 611 type 2 diabetic subjects, N= 803 non-diabetic subjects) using multivariate analysis of traditional risk factors and then adding MS, apoB and homeostatic model assessment for insulin resistance (HOMA-IR). Incremental value was tested with likelihood ratio testing. Beyond traditional risk, HOMA-IR [Tobit regression ratio 1.86 (p=0.002)], apoB [1.55 (p=0.001)] and MS [2.37 (p=0.007)] were independently associated with CAC. In nested models, HOMA-IR added value to apoB [1.72 (p=0.008)], MS [1.72 (p=0.011)] and both apoB and MS [1.64 (p=0.021)]. ApoB showed a similar pattern when added to HOMA-IR [1.51 (p=0.004)], MS [1.46 (p=0.005)] and both HOMA-IR and MS [1.48 (p=0.006)]. MS added to apoB [1.99 (p=0.032)], but not HOMA-IR [1.54 (p=0.221)] or both apoB and HOMA-IR [1.32 (p=0.434)]. In conclusion, insulin resistance estimates add value to MS and apoB in predicting CAC scores in DM and warrant further evaluation in clinic for identification of DM patients at higher risk for atherosclerotic cardiovascular disease.

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Disclosures

The authors have no conflicts of interest with respect to this manuscript.

Keywords

insulin resistance; apolipoprotein B; coronary artery calcification; type 2 diabetes

Levels of apoB lipoproteins are associated with IR and the MS [1]. It is unknown, however, if the presence of MS or the degree of IR represent independent tools for CVD risk stratification in DM beyond measurement of apoB or nonHDL-C. Therefore, we compared the association of MS, apoB lipoproteins and insulin resistance, estimated by the homeostasis model assessment for insulin resistance (HOMA-IR) with CAC in a DM sample. As a comparison, we performed similar analysis in non-diabetics in whom we have previously shown that both MS and HOMA-IR predict greater CAC [2]. We hypothesized that HOMA-IR and MS would add incremental value to apoB and nonHDL-C in predicting CAC scores in both DM and non-DM samples.

Methods

Details of the Penn Diabetes Heart Study (PDHS) and the Study of Inherited Risk of Coronary Atherosclerosis (SIRCA) 2-4 are described elsewhere. Both are single center, cross-sectional studies of subjects without clinical evidence of CVD. They were recruited at the University of Pennsylvania (Penn) and utilized the same clinical research center, research staff, electron-beam CT (EBCT) scanner, and biochemical laboratory. SIRCA subjects were recruited based on a family history of premature CVD excluding DM. PDHS subjects were recruited on the basis of having DM. Exclusion criteria included clinical CVD, elevated creatinine and, in SIRCA, the presence of diabetes. This report focuses on unrelated, Caucasian subjects (611 PDHS diabetic participants and 803 SIRCA non-diabetic participants).

Participants were evaluated at the Clinical and Translational Research Center at Penn after a 12-hour fast 2. Plasma levels of lipids were measured enzymatically (Cobas Fara II; Roche Diagnostic Systems, Somerville, NJ) in lipoprotein fractions after ultracentrifugation (β-quantification technique) in PDHS, and in whole plasma in SIRCA. For apoB and C-reactive protein (CRP; high-sensitivity), an immunoturbidimetric assay was used 5. Plasma insulin was measured by radioimmunoassay (Linco Research, St. Charles, MO) 2. The intra-assay and inter-assay CVs for insulin were 4.1% and 11.6%, respectively. HOMA-IR, an indirect measure of insulin resistance, was calculated in a fasting state [glucose (mmol/L) × insulin (μU/mL)/22.5] 6. Because the HOMA-IR2 calculation may be more robust than HOMA-IR in DM as it accounts for outlier values of glucose and insulin, we also confirmed our findings using the HOMA-IR2 approach (Spearman correlation of HOMA-IR2 and HOMA-IR = 0.98) and found no differences in results (data not shown). Laboratory test results were generated by personnel blinded to clinical characteristics and CAC scores of participants. Framingham risk scores (FRS), using total cholesterol, were calculated as described by Wilson *et al.* [7]. Subjects were classified as having MS using the revised NCEP definition (glucose cut-point 100 mg/dl) [8]. Global CAC scores, at EBCT, were quantified 9 according to the method of Agatston 10.

Data are reported as median (interquartile range (IQR)) or mean±standard deviation (SD) for continuous variables and as proportions for categorical variables. The crude association of apoB, nonHDL-C and HOMA-IR with lipid, metabolic, inflammatory parameters and each component of MS were examined by Spearman correlation and the Kruskal-Wallis test. Multivariable analysis of CAC scores was performed using Tobit conditional regression of natural log (CAC+1) because of the distribution of CAC data (many zero scores with a marked right skew) 9. Tobit regression models the dichotomous outcome of zero versus

non-zero and then assumes normality conditional on the presence of non-zero score data 11. The tobit model is designed to assess the relationship between explanatory variables and a censored dependent variable at one end, where many observations are clustered. We chose this modeling since the use of ordinary least-squares regression on such a non normal distribution such as CAC would produce biased estimates and invalid inference. Tobit modeling has otherwise similar assumptions about error distributions as the linear regression model. The association of MS (presence vs. absence), HOMA-IR (1 SD), apoB (1 SD) and nonHDL-C (1 SD) with CAC was assessed in Tobit models with confounding risk factors: age, gender, medications and risk factors including hypertension (defined as SBP>140 or DBP>90 mmHg12 or use of anti-hypertensive therapy), dyslipidemia (defined as serum total cholesterol > 5.18 mmol/L, LDL cholesterol>2.59 mmol/L, triglyceride> 1.70 mmol/L or use of dyslipidemia therapy) alcohol use, exercise, and CRP. We also tested FRS in place of hypertension, hyperlipidemia and tobacco use and did not find differences in the results (not shown). Finally, we applied likelihood ratio tests (LRT) in nested models to assess the value of each parameter (HOMA IR, MS, apoB, nonHDL-C) relative to each other in predicting CAC. Statistical analyses were performed using Stata 10.0 software (Stata Corp, College Station, TX).

Results

Table 1 shows the characteristics of PDHS diabetics (PDHS) and non-diabetics (SIRCA). Diabetics were older, predominantly males and more obese. As expected, LDL cholesterol levels were lower in diabetic subjects reflecting their higher statin use. As expected, HOMA IR values were higher in DM (15% of diabetics were on insulin and excluded from HOMA-IR calculation). NCEP-defined MS was present in 77% of DM and 26% of non diabetics. Consistent with greater CVD risk, FRS and CAC scores were higher in DM.

The correlation of both HOMA-IR and apoB with other risk factors were broadly similar across diabetes status (Table 2). Interestingly, HOMA-IR had the strongest correlations with metabolic and inflammatory risk factors while apoB showed stronger relationship with atherogenic lipoproteins and the FRS. Although both HOMA-IR and apoB were associated with the MS, the strength and extent of association with individual MS components differed such as a strong association of HOMA-IR with waist, presence of M and HDL levels, whereas apoB had the strongest association with triglycerides (data not shown). These findings suggest that HOMA-IR and apoB may capture distinct information regarding metabolic CVD risk. NonHDL-C was highly correlated with apoB (r^2 ~of 0.8). Indeed, findings were similar for nonHDL-C and apoB, and therefore only data for apoB is presented throughout the manuscript.

In DM, MS, HOMA IR, and apoB were associated with CAC scores after adjusting for traditional risk factors, lipid lowering and diabetes medications. (Table 3, **Model 1**). In non-diabetics as published [2,5], a similar pattern of association was seen for MS, HOMA IR and apoB.

When MS (Table 3, **upper panel**) was added to apoB, MS remained independently associated with CAC in both DM and non-DM. When MS was added to HOMA-IR, however, there was an attenuation of MS association with CAC in DM but not in non-diabetics. Further, when MS was added to fully adjusted model containing both HOMA-IR and apoB, there was loss of MS relationship with CAC in diabetics and in non diabetics.

When HOMA-IR (Table 3, **middle panel**) was added to MS, HOMA-IR remained independently associated with CAC in both DM and in non-DM. Similarly, when HOMA-IR was added to apoB, it remained independently associated with CAC in both DM and non-

DM (Table 3). In contrast to MS, when HOMA-IR was added to a fully-adjusted model containing both MS and apoB, HOMA-IR remained associated with CAC in both DM nd in non-DM. These results did not change when plasma adiponectin, interleukin-6 and leptin were added to this model (data not shown).

When apoB (Table 3, **lower panel**) was added to HOMA IR, apoB remained associated with CAC in both DM and non-DM, and a similar relationship was observed when apoB was added to MS in DM and non-DM. When apoB was added to MS and HOMA-IR, apoB continued to be a significant predictor of CAC in DM and in non-DM.

In general, MS, HOMA-IR and apoB added incrementally to traditional risk factors in predicting CAC (Table 4). However, in both diabetics and non-diabetics, apoB and HOMA-IR tended to add more value than MS in predicting CAC scores. In fact, MS did not add to HOMA-IR in predicting CAC in DM.

Discussion

We addressed the hypothesis that HOMA-IR and MS would add value to atherogenic apoB lipoproteins as well as traditional risk factors in predicting subclinical coronary atherosclerosis in DM measured by CAC. First, we found that MS and HOMA-IR, as well as apoB were each associated with CAC independent of traditional risk factors in both diabetic and non diabetic subjects. Second, in predicting higher CAC scores, we found that HOMA-IR added value to MS and apoB levels while apoB levels added to MS and HOMA-IR in both diabetics and non diabetics. This suggests complimentary value for HOMA-IR and apoB in CAC risk determination across a wide cardiometabolic spectrum. Finally, MS, in contrast, did not add value beyond HOMA-IR and apoB suggesting that it may not add independent value in assessing CVD risk when more direct measures of atherogenic lipoproteins and insulin resistance are determined.

CVD is the cause of death in up to 80% of individuals with DM. Despite aggressive risk factor management on par with secondary prevention strategies for those with established clinical CVD [12,13], there still continues to be higher than expected incidence of CVD within this population. However, strategies may not be optimal with current risk algorithms. For example, the FRS has been well-validated in the general population [7], but there is debate regarding its accuracy in CVD predicting in DM. This likely reflects low overall prevalence of DM in the Framingham Study and the failure of FRS to include triglyceride-rich atherogenic particles. Given these limitations of FRS, and the modest adoption of risk scores into clinical practice, improved markers of atherosclerotic CVD in DM patients are required.

One approach to improved risk prediction in DM is through improved measurement of triglyceride-rich atherogenic lipoprotein particles which are more abundant in DM than in non-DM. Indeed, apoB, a measure of total atherogenic particles as well as LDL particles (LDL-P), has surpassed LDL-C as a predictor of CHD events and residual risk on therapy as shown in most [14,15] but not all studies [16,17]. Further, we reported recently that apoB and non-HDL-C, but not LDL-C, are independently associated with CAC in DM [5]. Here, we extend these findings by demonstrating that apoB levels add value to the NCEP-defined MS as well as to HOMA-IR in predicting CAC scores in both DM and non-DM patients. This is not surprising given that apoB and HOMA-IR have modest overlap in their relationship with established CVD risk factors (Table 2) and therefore are likely to capture distinct information regarding cardio-metabolic risk. Our findings are broadly consistent with a recent joint consensus statement from the American Diabetes Association and American College of Cardiology that recommends incorporating apoB measurement in managing patients with cardiometabolic risk [18].

MS definitions have emerged as clinical tools for improved CVD risk prediction in the non-diabetic population. We and others have shown that MS is also a strong predictor of CAC in non-DM samples [2,19]. Although DM patients are often considered homogeneous with respect to having the MS, it appears that the presence as well as the extent of MS abnormality in DM may be a strong indicator of CVD risk. For example, Bonora et al. demonstrated a five-fold increase in CVD when MS was present in DM [20]. In our current analysis, MS was associated with CAC in DM. However, this association was attenuated, especially in DM, when apoB levels and HOMA-IR data were included. Therefore, MS may be a useful tool for identifying high-risk DM patients, but it may not add value when direct measures of atherogenic lipoproteins and insulin resistance are available.

Our finding that HOMA-IR was associated with CAC beyond traditional risk factors, MS, and atherogenic lipoproteins in DM is novel and intriguing. Use of HOMA-IR and other fasting-insulin measures have been criticized in DM because they lack sensitivity for IR relative to gold-standard techniques such as euglycemic clamps [21]. However, others have demonstrated a robust relationship, albeit attenuated relative to that in non-DM subjects, between HOMA-IR and clamp data in DM [22]. Our findings suggest that HOMA-IR is capturing information beyond the NCEP definition of MS and may be helpful in identifying patients at higher CVD risk. Indeed, recently Caccamo et al. showed that HOMA-IR levels predicted poorer outcomes in patients with acute coronary syndrome beyond traditional risk factors [23]. Our observation that HOMA-IR also predicted CAC scores in DM beyond plasma levels of adiponectin, leptin, hs-CRP and IL-6 suggests that it defines aspects of CVD risk that are not captured by multiple, non-insulin based biomarkers of cardiometabolic dysfunction in DM. Whether insulin-based measures of IR predict incident CVD in DM requires further assessment in the effort to develop more refined strategies for identifying DM patients at highest CVD risk.

MetSyn is a global integration of clinical characteristics which may relate to insulin resistance (IR) and atherogenic risk. However, it may be somewhat redundant when direct, refined measures of IR and atherogenic dyslipidemia are present. Our findings suggest this may be the case. The utility of metabolic syndrome, however, may be maintained within current clinical practice in the context that IR measures are not routinely used nor standardized for measurement and metabolic syndrome added value to apoB.

Our study has several limitations. Analyses were cross-sectional, thus causal and longitudinal relationships were not addressed. We also did not examine clinical outcomes, although our data is largely consistent with clinical outcomes studies [23-25]. Given insulin secretion [26] and CAC [27] variability by race, our findings cannot be generalized beyond Caucasians. In addition, CAC is an estimate [28], and not a direct measure of coronary atherosclerosis, thus it may fail to detect some coronary plaques. Despite this limitation, however, CAC scores are strong, independent predictors of events [29], including in diabetes [30].

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Table 1

Characteristics of study sample

Variable	Diabetes Mellitus	
	Yes (N=611)	No (N=803)
	Median (IQR)	Median (IQR)
Age (median age; full range)	60 (36-77)	48 (20-73)
Male	436 (71.4 %)	424 (52.8 %)
Alcohol use	357 (58.4 %)	544 (67.8 %)
Current smoking	51 (8.4 %)	91 (11.3 %)
HDL Cholesterol (mmol/l)	1.17 (0.99-1.37)	1.24 (1.01-1.53)
Male Female	1.1(0.9-1.2) 1.3(1.1-1.6)	1.1(0.9-1.3) 1.5(1.2-1.8)
Total Cholesterol (mmol/l)	4.51 (3.94-5.13)	5.31 (4.58-5.91)
Triglycerides (mmol/l)	1.51 (1.04-2.23)	1.32 (0.98-1.80)
LDL Cholesterol (mmol/l)	2.51 (2.04- 3.08)	3.26 (2.67-3.83)
Apolipoprotein B (g/l)	0.82 (0.71-0.94)	0.98 (0.84-1.14)
Blood pressure (mmHg)		
Systolic	131 (122-140)	126 (117-136)
Diastolic	76 (71-81)	77 (72-84)
Body Mass Index (kg/m2)	32 (28-36)	27 (24-30)
Male Female	31 (28-35) 34 (29-38)	27 (25-30) 26 (23-30)
Waist circumference (inches)	42 (39-46)	35 (32-39)
Metabolic Syndrome	468 (76.6 %)	207 (25.78 %)
Leptin (µg/l)	11.6 (6.5-20.9)	8.4 (4.5-16.4)
Adiponectin (µg/ml)	9.1 (6.12-14.87)	16.3 (11.58-24.55)
HOMA IR	4.38 (2.9-6.7)	1.43 (0.9-2.1)
Hs-C reactive Protein (mg/dl)	1.6 (0.8-3.4)	1.2 (0.5-2.6)
Interleukin-6 (pg/ml) Total	1.32 (0.8-2.1)	1.3 (0.8-1.9)
Male Female	1.2(0.8-2) 1.4(0.7-2.3)	1.2(0.7-1.8) 1.2(0.8-2)
Medications		
Statin	351 (57.5 %)	112 (13.9 %)
Niacin	34 (5.6 %)	23 (2.9 %)
Fibrate	60 (9.9 %)	9 (1.1 %)

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Variable	Diabetes Mellitus	
	Yes (N=611)	**No (N=803)**
	Median (IQR)	**Median (IQR)**
Insulin	91 (14.9 %)	0
Metformin	390 (63.8 %)	0
Thiazolidinediones	167 (27.3 %)	0
Sulfonylureas	246 (40.3 %)	0
Hormone Replacement	276 (45.1 %)	226 (28.2 %)
Therapy (women)		
Coronary artery calcium		
Median score (IQR)	89 (1-456)	3 (0-45)
Mean score (±SD)	424±795	87±266
Zero Score	24.7 %	31.1%
10-year Framingham LDLRisk	13 % (9-18)	5 % (3-7)
10-year Framingham TC Risk	13 % (8-20)	5 % (3-8)

For T2D, N=436 males and 175 females; for non-diabetic, N=424 males and 379 females. T2D subjects on insulin were excluded for calculation of homeostasis model assessment of insulin resistance (HOMA-IR), yielding an N=513.

CAC = Coronary artery calcification; CRP = C reactive protein; FRS= Framingham Risk Score; HDL= High density Lipoprotein; HOMA IR= Homeostasis model assessment of insulin resistance; HRT = hormone replacement therapy; IQR = Inter quartile range; LDL = Low density lipoprotein.

Table 2

Spearman Correlations of HOMA IR and Apolipoprotein B with Lipid, Metabolic and Inflammatory variables

	Diabetes Mellitus			
Variable	**Yes (N=611)**		**No (N=803)**	
	HOMAIR	**Apo-B**	**HOMAIR**	**Apo-B**
Total cholesterol	0.03	0.77**	0.07*	0.77**
Triglycerides	0.38**	0.47**	0.39**	0.50**
LDL cholesterol	-0.01	0.79**	0.10**	0.78**
HDL cholesterol	-0.31**	-0.21**	-0.32**	-0.20**
Non HDL cholesterol	0.16**	0.87**	0.22**	0.87**
Systolic Blood pressure	0.14**	0.05	0.32**	0.20**
Body Mass Index	0.43**	0.07	0.50**	0.23**
Waist (inches)	0.41**	0.08*	0.51**	0.25**
Framingham risk	0.06	0.38**	0.27**	0.49**
Hs C reactive protein	0.22**	0.16**	0.29**	0.24**
Interleukin-6	0.26**	0.02	0.30**	0.12**
Leptin	0.42**	0.03	0.34**	0.18**
Adiponectin	-0.28**	-0.20**	-0.27**	-0.15**
ApoB	0.20**	-	0.25**	-
HOMA IR	-	0.20**	-	0.25**

HOMA-IR = homeostasis model assessment of insulin resistance; for type 2 diabetic subjects, N=513; subjects on insulin excluded. HDL= High density Lipoprotein; LDL = Low density lipoprotein; CRP = C reactive protein.

* P<0.05

** P<0.01

Table 3

Association of Metabolic syndrome, HOMA IR and plasma levels of Apolipoprotein B with coronary calcium in multivariable models

	Diabetes mellitus	
	Yes (N=611)	No (N=803)
Variable	Tobit Ratio (95%CI) (P-value)	Tobit Ratio (95%CI) (P-value)
MetSyn		
Model 1	2.37 (1.27-4.41) (p=0.007)	2.15 (1.43-3.24) (p<0.001)
Model 2 (HOMA IR)	1.54 (0.77-3.06) (p=0.221)	1.66 (1.08-2.55) (p=0.021)
Model 3 (ApoB)	1.99 (1.06-3.73) (p=0.032)	1.75 (1.24-2.65) (p=0.009)
Model 4 (HOMA IR & ApoB)	1.32 (0.66-2.64) (p=0.434)	1.40 (0.91-2.16) (p=0.126)
HOMA IR		
Model 1	1.86 (1.25-2.78) (p=0.002)	1.84 (1.40-2.42) (p<0.001)
Model 2 (MetSyn)	1.72 (1.13-2.62) (p=0.011)	1.66 (1.24-2.20) (p=0.001)
Model 3 (ApoB)	1.72 (1.15-2.57) (p=0.008)	1.66 (1.26-2.19) (p<0.001)
Model 4 (MetSyn & ApoB)	1.64 (1.08-2.49) (p=0.021)	1.56 (1.17-2.07) (p=0.002)
ApoB		
Model 1	1.55 (1.19-2.01) (p=0.001)	1.58 (1.33-1.90) (p<0.001)
Model 2 (HOMA IR)	1.51 (1.14-1.99) (p=0.004)	1.51 (1.26-1.81) (p<0.001)
Model 3 (MetSyn)	1.46 (1.12-1.91) (p=0.005)	1.50 (1.25-1.80) (p<0.001)
Model 4 (HOMA IR & MetSyn)	1.48 (1.12-1.96) (p=0.006)	1.47 (1.22-1.76) (p<0.001)

Results of Tobit regression are presented as the ratio of increase in coronary calcium score for one standard deviation increase in apoB; standard deviation for pooled cohort allowing comparison across diabetes status. Standard deviation for apoB in diabetics was 17.84 and 22.83 for non diabetics.

Model 1 includes age, gender, medications and risk factors. Medications included statins, niacin, insulin, metformin, thiazolidinediones. Risk factors included hypertension, hyperlipidemia, tobacco use, alcohol use, exercise and high sensitivity C-reactive protein.

Models 2-4 include model 1 and the corresponding variable as denoted within the parenthesis in the table.

HOMA-IR = homeostasis model assessment of insulin resistance. For HOMA-IR, type 2 diabetic subjects on insulin were excluded from analysis, yielding N=513.

Table 4

Relative value of metabolic syndrome, HOMA IR & Apolipoprotein B in predicting calcium scores

Variable	Diabetes Mellitus	
	Yes (N=611)	No (N=803)
	Chi square (p value)	Chi square (p value)
MetSyn added to model *	7.44 (p<0.001)	13.39 (p<0.001)
ApoB added to model *	10.80 (p<0.001)	25.45 (p<0.001)
HOMAIR added to model *	9.29 (p<0.001)	18.96 (p<0.001)
HOMAIR added to MetSyn in model *	6.45 (p=0.011)	11.76 (p<0.001)
MetSyn added to HOMAIR in model *	1.51 (p=0.2198)	5.32 (p=0.021)
ApoB added to MetSyn in model *	7.98 (p<0.001)	18.99 (p<0.001)
MetSyn added to ApoB in model *	4.62 (p=0.0298)	6.93 (p<0.001)
ApoB added to HOMAIR in model *	8.55 (p<0.001)	19.83 (p<0.001)
HOMAIR added to ApoB in model *	7.03 (p<0.001)	13.25 (p<0.001)

Likelihood ratio testing was applied in nested Tobit models to assess the incremental value of metabolic syndrome, HOMA IR and ApoB, and vice versa, in predicting CAC scores.

HOMA-IR = homeostasis model assessment of insulin resistance. MetSyn = metabolic syndrome. For models including HOMA-IR in type 2 diabetic subjects, N=513; subjects on insulin excluded.

* All models included age, gender, niacin, statin, metformin, thiazolidinediones, insulin, hypertension, hyperlipidemia (based on NCEP criteria), alcohol use, tobacco use, exercise and C reactive protein