Differential Associations of Oral Glucose Tolerance Test–Derived Measures of Insulin Sensitivity and Pancreatic β-Cell Function With Coronary Artery Calcification and Microalbuminuria in Type 2 Diabetes

Claire K. Mulvey,[1] Ann M. McNeill,[2] Cynthia J. Girman,[2] Timothy W. Churchill,[1] Karen Terembula,[1] Jane F. Ferguson,[1] Rachana Shah,[3] Nehal N. Mehta,[1] Atif N. Qasim,[4] Michael R. Rickels,[5] and Muredach P. Reilly[1]

OBJECTIVE

We evaluated relationships of oral glucose tolerance testing (OGTT)–derived measures of insulin sensitivity and pancreatic β-cell function with indices of diabetes complications in a cross-sectional study of patients with type 2 diabetes who are free of overt cardiovascular or renal disease.

RESEARCH DESIGN AND METHODS

A subset of participants from the Penn Diabetes Heart Study (*n* = 672; mean age 59 ± 8 years; 67% male; 60% Caucasian) underwent a standard 2-h, 75-g OGTT. Insulin sensitivity was estimated using the Matsuda Insulin Sensitivity Index (ISI), and β-cell function was estimated using the Insulinogenic Index. Multivariable modeling was used to analyze associations between quartiles of each index with coronary artery calcification (CAC) and microalbuminuria.

RESULTS

The Insulinogenic Index and Matsuda ISI had distinct associations with cardiometabolic risk factors. The top quartile of the Matsuda ISI had a negative association with CAC that remained significant after adjusting for traditional cardiovascular risk factors (Tobit ratio −0.78 [95% CI −1.51 to −0.05]; *P* = 0.035), but the Insulinogenic Index was not associated with CAC. Conversely, the highest quartile of the Insulinogenic Index, but not the Matsuda ISI, was associated with lower odds of microalbuminuria (OR 0.52 [95% CI 0.30–0.91]; *P* = 0.022); however, this association was attenuated in models that included duration of diabetes.

CONCLUSIONS

Lower β-cell function is associated with microalbuminuria, a microvascular complication, while impaired insulin sensitivity is associated with higher CAC, a predictor of macrovascular complications. Despite these pathophysiological insights, the Matsuda ISI and Insulinogenic Index are unlikely to be translated into clinical use in type 2 diabetes beyond established clinical variables, such as obesity or duration of diabetes.

Diabetes Care 2014;37:124–133 | DOI: 10.2337/dc12-1880

[1]Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[2]Department of Epidemiology, Merck Research Laboratories, North Wales, PA
[3]Division of Pediatric Endocrinology, Children's Hospital of Philadelphia, Philadelphia, PA
[4]Division of Cardiology, University of California, San Francisco, San Francisco, CA
[5]Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Corresponding author: Muredach P. Reilly, muredach@mail.med.upenn.edu.

Received 14 September 2012 and accepted 9 August 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-1880/-/DC1.

The primary defects observed in type 2 diabetes are insulin resistance and inadequate insulin secretion by pancreatic β-cells (1). By the time clinical hyperglycemia develops, both insulin sensitivity and β-cell function have already declined. Debate exists over the relative importance of these two abnormalities, which are distinct but integrated in the clinical manifestations of type 2 diabetes (2). Insulin sensitivity and β-cell function may have independent relations to microvascular and macrovascular complications.

Microvascular damage to the renal glomerulus leads to diabetic nephropathy, a significant cause of renal failure (3). As with other microvascular complications, hyperglycemia is a major determinant of nephropathy, with intensive glycemic control reducing the burden of the disease (4). Previous studies (5–7) are inconsistent regarding the relationship between insulin resistance and microalbuminuria, a hallmark of early diabetic nephropathy. The association between β-cell dysfunction and microalbuminuria has not been well studied.

The association between type 2 diabetes and cardiovascular disease (CVD) is strong, but the precise mechanisms by which diabetes increases the formation of atherosclerotic plaque are incompletely understood. Unlike microvascular complications, intensive glucose lowering may not reduce cardiovascular events (8–10). The insulin resistance milieu of type 2 diabetes is closely associated with metabolic syndrome—a clustering of risk factors that includes hypertension, abdominal adiposity, dyslipidemia, and inflammation. However, because diabetes confers cardiovascular risk beyond traditional risk factors, the degree of insulin resistance may independently affect macrovascular complications (11). Surrogate measures of insulin resistance have been associated with atherosclerotic burden in several studies (12–14). Previous studies were generally conducted in subjects with impaired glucose tolerance, impaired fasting glucose, or both, although we performed a preliminary study in patients with type 2 diabetes (15). Most studies, including our prior work, used static, fasting measures of insulin resistance, such as the homeostatic model assessment (HOMA)-estimated insulin resistance (HOMA-IR), as opposed to dynamic parameters, for example, those derived from oral glucose tolerance testing (OGTT).

OGTT has utility for evaluating insulin sensitivity and β-cell function during glucose administration via a physiological route. In particular, the Matsuda Insulin Sensitivity Index (ISI) is an OGTT-derived surrogate of whole-body insulin sensitivity (16), whereas the Insulinogenic Index measures first-phase insulin secretion and β-cell function (17). It is uncertain whether these OGTT parameters are associated with diabetes complications or if the pattern of association is similar for these two indices, which reflect different but interrelated facets of type 2 diabetes. Also unclear is whether OGTT measures are superior to static parameters (e.g., HOMA indices) or if they provide incremental information regarding the risk of complications independent of traditional risk factors and metabolic syndrome.

We therefore examined associations of OGTT-derived parameters with two indices of diabetes complications: coronary artery calcification (CAC) and microalbuminuria. CAC is strongly correlated with the degree of subclinical atherosclerosis by histopathology (18) and angiography (19) and has utility for the prediction of cardiovascular events (20). Persistent microalbuminuria increases risk for end-stage kidney disease two- to fourfold (21). In this article we evaluate associations between insulin sensitivity (measured by the Matsuda ISI) and β-cell function (measured by the Insulinogenic Index) with CAC and microalbuminuria, and we compare findings to those of HOMA indices, in a cross-sectional study of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Details of the Penn Diabetes Heart Study (PDHS) have been published previously (22). PDHS is a cross-sectional study of factors associated with CAC in subjects aged 35–75 years. Participants were recruited at the University of Pennsylvania (Penn) on the basis of a clinical diagnosis of type 2 diabetes, defined as fasting blood glucose >126 mg/dL, 2-h postprandial glucose >200 mg/dL, or use of oral hypoglycemic agents or insulin in subjects >40 years of age, with the diabetes diagnosis made after age 35. Exclusion criteria included clinical CVD and serum creatinine >2.5 mg/dL. This article focuses on participants recruited between 2007and 2011 who underwent OGTT. Of the 990 subjects eligible based on the enrollment period, 833 completed OGTT, while 157 subjects did not complete OGTT because of failure to obtain consistent vascular access or because they declined to participate in the substudy. Supplementary Table 1 summarizes the baseline characteristics of subjects who did not undergo OGTT. This study was approved by Penn's institutional review board. All participants gave informed consent.

OGTT Protocol

Subjects were evaluated at Penn's Clinical and Translational Research Center after an overnight fast. Subjects were instructed not to take medication, including insulin, the morning of the study. A 2-h OGTT was performed with a 75-g glucose load; blood samples were collected at baseline and 30, 60, and 120 min.

Indices of β-Cell Function and Insulin Sensitivity

Participants who underwent OGTT but had fasting glucose >200 mg/dL or insulin >125 μIU/mL were excluded from analysis because of concern for glucotoxicity and subsequent impaired β-cell function, incomplete overnight fast, or exogenous insulin use the morning of OGTT. We also excluded subjects with a history of gastric bypass surgery (23). The Insulinogenic Index was calculated as the ratio of the increment of plasma insulin (micro–international units per milliliter) to the increment in glucose (milligrams per deciliter) during the first 30 min of OGTT (ΔI_{30} /ΔG_{30}) (17). We estimated whole-body insulin sensitivity by calculating the Matsuda ISI using the following

formula (with glucose and insulin values as indicated above): 10,000 / $(G_0 \times I_0 \times G_m \times I_m)^{0.5}$, where G_0 and I_0 are values of glucose and insulin before the glucose load and G_m and I_m are mean values after the glucose load (16). The Matsuda ISI correlates well with insulin sensitivity as measured by a hyperinsulinemic-euglycemic clamp, the gold standard, even in type 2 diabetes (16). As a complementary measure of hepatic insulin resistance, we also calculated fasting HOMA-IR: (glucose [mg/dL] × insulin [μIU/mL])/405 (24). In addition, as an alternative measure of β-cell function we calculated fasting HOMA of β-cell function (HOMA-B) (360 × insulin [μIU/mL]/[glucose {mg/dL} – 63]) in the subset of participants not receiving insulin therapy (n = 530); HOMA-B is not valid in those taking insulin (25). We selected HOMA indices for comparative analysis based on their performance in previous investigations and their utility in large-scale, population-based studies.

Statistical Analysis

Data are reported as median (interquartile range) for continuous variables and proportions for categorical variables. Because the Insulinogenic Index and Matsuda ISI are not normally distributed (Supplementary Fig. 1), we divided participants into quartiles of these data. We evaluated crude associations across quartiles of OGTT measures with clinical, lipid, metabolic, and inflammatory parameters using a nonparametric test for trend across ordered groups (nptrend using Stata software). We analyzed associations of quartiles of the Insulinogenic Index and Matsuda ISI in incremental multivariable modeling of microalbuminuria and CAC data, including multiple risk factors in full models. In sensitivity analyses, we transformed the Insulinogenic Index (inverse normal-transformed to accommodate negative values) and Matsuda ISI (natural log-transformed) (Supplementary Fig. 1) to facilitate modeling as continuous variables.

We performed logistic regression and report multivariable-adjusted associations for the top versus bottom quartiles of either the Insulinogenic Index or Matsuda ISI with the presence of microalbuminuria, defined as spot urine albumin-to-creatinine ratio ≥30 mg/g. We evaluated associations with microalbuminuria in incremental models, adjusting for potential confounders, including model 1 (age, sex, race); model 2 (model 1 plus history of hypertension, HbA_{1c}, medications, and Framingham risk score [FRS] [26]); and model 3 (model 2 plus duration of diabetes). To examine the multivariable-adjusted associations between CAC and the top versus bottom quartiles of either the Insulinogenic Index or Matsuda ISI, our primary approach was to perform Tobit conditional regression of natural log (CAC + 1). Tobit regression is suited to the distribution of CAC data (many zeros and a marked right skew) (27) because it combines logistic regression for the dichotomous outcome of "presence of CAC" (any CAC vs. CAC score of zero) with linear regression (of log-transformed CAC) when CAC is present to produce a single estimate for the relationship of risk factors with CAC. We tested associations with CAC in incremental models in model 1 (age, sex, race); model 2 (model 1 plus exercise, high-sensitivity C-reactive protein [hsCRP], FRS, current alcohol use, medications, and microalbuminuria); and model 3 (model 2 plus duration of diabetes). We included interaction terms for race and sex in fully adjusted models, but these were not significant (data not shown). Trends across quartiles in logistic and Tobit regression models were assessed using ordinal variables based on the median value of each Insulinogenic Index or Matsuda ISI quartile. Testing of likelihood ratio in nested models and Akaike information criteria (AIC) analysis in nonnested models were used to compare the goodness of fit of the Matsuda ISI versus the Insulinogenic Index. In complementary analyses we performed separate logistic regression of the "presence of CAC" and linear regression of the "burden of CAC" (log of CAC for 448 patients with CAC scores >0). Two-tailed $P < 0.05$ was considered statistically significant. Analyses were performed using STATA 12.0 software (Stata Corp., College Station, TX).

RESULTS

Characteristics of the Study Population

Of the 833 PDHS participants who underwent OGTT, we excluded subjects because of a baseline glucose >200 mg/dL (n = 81), baseline insulin >125 μIU/mL (n = 3), an extreme negative outlier for the Insulinogenic Index (n = 1), a history of bariatric surgery (n = 6), or missing covariate data (n = 70). Compared with subjects who completed OGTT, excluded subjects had higher HbA_{1c} and a longer duration of diabetes and were more likely to be taking insulin and have metabolic syndrome (Supplementary Table 1). The characteristics of the 672 remaining participants included in analysis are noted in Supplementary Table 1. The median duration of diabetes was 6 years, and 21% of participants were taking insulin.

Differential Associations of the Insulinogenic Index and the Matsuda ISI With Cardiovascular Risk Factors and Measures of Diabetes Control

The Insulinogenic Index and Matsuda ISI were only modestly correlated with each other (Spearman correlation $\rho = -0.29$; $P < 0.001$). The Insulinogenic Index did not differ in univariate analyses by either race or sex, whereas the Matsuda ISI differed by race but not by sex, with a higher percentage of Caucasians in the quartile with the lowest insulin sensitivity. As expected, HOMA-IR was inversely correlated with the Matsuda ISI ($\rho = -0.91$; $P < 0.001$), while HOMA-B was positively correlated with the Insulinogenic Index ($\rho = 0.56$; $P < 0.001$) in the subset of participants not taking exogenous insulin (n = 530).

In univariate analysis, subjects with the most depressed β-cell function (as reflected by the lowest quartile of the Insulinogenic Index) had a longer duration of diabetes, higher HbA_{1c}, and higher baseline glucose, but lower baseline insulin, C-peptide, and proinsulin, compared with subjects in the top quartile (Table 1). Subjects in the lowest Insulinogenic Index quartile also had lower BMI and waist circumference, less insulin resistance, and lower leptin levels. They had a less atherogenic lipid profile, with lower LDL, lower

Table 1—Characteristics of the study sample across Insulinogenic Index (IGI) quartiles (each *n* = 168)

Variable	IGI quartile 1	IGI quartile 2	IGI quartile 3	IGI quartile 4	*P* value*
IGI	0.05 (0.01–0.08)	0.16 (0.13–0.20)	0.32 (0.28–0.38)	0.80 (0.61–1.21)	<0.001
Age (years)	59 (54–65)	60 (54–66)	61 (54–65)	60 (53–64)	0.51
Female, %	34.5	31.0	31.6	36.3	0.72
Race, %					0.47
Caucasian	56.6	69.6	61.3	54.2	
African American	36.3	25.0	35.1	39.9	
Other	7.1	5.4	3.6	6.0	
Blood pressure (mmHg)					
Systolic	130 (121–141)	131 (121–144)	131 (121–140)	129 (120–141)	0.79
Diastolic	75 (70–81)	74 (71–81)	76 (72–83)	76 (71–83)	0.048
Total cholesterol (mg/dL)	160 (140–185)	158 (140–180)	162 (143–189)	165 (146–193)	0.17
HDL cholesterol (mg/dL)	45 (38–55)	45 (38–54)	43 (37–52)	42 (36–52)	0.027
Triglycerides (mg/dL)	99 (74–153)	110 (80–159)	117 (80–167)	116 (85–164)	0.022
LDL cholesterol (mg/dL)	86 (72–105)	86 (72–107)	91 (73–113)	92 (77–112)	0.029
BMI (kg/m^2)	30.2 (27.0–36.5)	31.0 (27.8–34.7)	32.9 (29.7–36.2)	33.7 (30.3–38.0)	<0.001
Waist circumference (cm)	103 (94–114)	104 (94–112)	109 (99–118)	109 (99–121)	<0.001
Metabolic syndrome, %	70.2	79.2	86.3	81.0	0.005
Duration of diabetes (years)	10 (5–16)	8 (4–13)	5 (2–10)	4 (1–7)	<0.001
HbA_{1c} (%)	7.0 (6.5–8.1)	6.5 (6.0–7.4)	6.5 (6.0–7.2)	6.1 (5.8–6.6)	<0.001
HbA_{1c} (mmol/mol)	53 (48–65)	48 (42–57)	48 (42–55)	43 (40–49)	<0.001
Glucose (mg/dL)	128 (106–153)	123 (105–144)	116 (103–136)	103 (93–118)	<0.001
Insulin (μIU/mL)	12.8 (9.0–25.4)	13.6 (9.5–18.5)	15.9 (11.3–22.5)	18.6 (12.6–27.2)	<0.001
Matsuda ISI	3.34 (2.13–4.71)	2.60 (2.00–4.07)	2.38 (1.66–3.13)	1.92 (1.26–2.94)	<0.001
HOMA-IR	4.0 (2.7–7.1)	4.1 (2.6–6.3)	4.5 (3.1–7.2)	4.7 (3.0–7.6)	0.044
HOMA-B%†	63.0 (41.4–93.4)	76.6 (55.1–107.7)	119.5 (84.8–155.3)	175.5 (118.9–246.0)	<0.001
C-peptide (ng/mL)	2.1 (1.3–3.3)	2.8 (2.0–3.5)	3.2 (2.4–3.9)	3.7 (2.6–4.5)	<0.001
Leptin (ng/mL)	11.6 (6.3–25.2)	13.0 (7.2–22.3)	16.1 (8.1–29.2)	18.2 (11.8–29.5)	<0.001
Proinsulin (pM)	16.4 (11.6–25.6)	23.9 (14.0–32.7)	23.8 (17.0–35.6)	25.1 (15.8–36.3)	<0.001
Current tobacco use, %	14.3	12.5	8.9	7.7	0.031
Current alcohol use, %	51.8	53.6	48.8	53.0	0.82
Exercise, %	61.9	66.7	60.7	62.5	0.69
10-year Framingham risk (%)‡	13 (8–20)	13 (10–20)	13 (9–20)	13 (9–20)	0.25
C-reactive protein (mg/L)	1.43 (0.73–3.72)	1.26 (0.69–3.36)	1.97 (0.84–4.91)	2.40 (0.89–5.98)	0.002
Antiplatelet medications, %					
Aspirin	39.3	50.6	44.1	43.5	0.73
Antihypertensive medications, %					
ACE inhibitor	64.9	70.2	59.5	64.3	0.45
β-Blocker	12.5	13.1	16.1	22.6	0.009
Calcium channel blocker	19.1	18.5	16.1	17.9	0.65
Lipid-lowering medications, %					
Statins	61.9	64.3	54.2	59.5	0.31
Niacin	6.6	7.1	9.5	10.1	0.17
Fibrates	6.6	7.7	4.8	3.0	0.082
Diabetes medications, %					
Metformin	71.4	70.2	69.6	60.7	0.042
Sulfonylureas	35.1	39.3	26.2	22.6	0.002
Thiazolidinediones	28.6	25.0	16.7	11.3	<0.001
Exenatide	7.1	8.3	4.2	3.6	0.065
Sitabliptin	12.5	9.5	10.7	9.5	0.47
Insulin	41.1	22.0	16.7	4.8	<0.001
Serum creatinine (mg/dL)	0.90 (0.75–1.05)	0.90 (0.75–1.04)	0.88 (0.77–1.01)	0.90 (0.74–1.00)	0.53
Microalbumin/urine creatinine ratio (mg/g)	19.0 (10.8–42.4)	17.3 (11.0–35.1)	16.2 (11.4–38.1)	16.4 (10.3–28.9)	0.030
Microalbuminuria, %§	36.3	30.4	30.4	23.8	0.018
CAC score	27 (0–257)	85 (0–341)	41 (0–288)	26 (0–171)	0.25
CAC score >0, %	64.3	72.6	72.0	57.7	0.21

Data are median (interquartile range) unless otherwise indicated. **P* values are from the nonparametric test for trend across ordered groups, an extension of the Wilcoxon rank-sum test. †HOMA-B% calculated only for the subsample of participants not taking exogenous insulin. ‡Total cholesterol 10-year Framingham risk percentage. §Microalbuminuria defined as a spot urine albumin-to-urine creatinine ratio ≥30 mg/g.

triglycerides, and higher HDL, perhaps because of lower BMI and greater use of thiazolidinediones and statins.

Subjects with the most impaired insulin sensitivity (as reflected by the Matsuda ISI) in the lowest quartile had higher measures of adiposity, including higher BMI, waist circumference, and leptin levels (Table 2). They were also more likely to meet criteria for metabolic syndrome and had a more atherogenic lipid profile, with higher triglycerides and lower HDL. Subjects in the lowest quartile of the Matsuda ISI had higher HbA_{1c} and higher baseline levels of glucose, insulin, C-peptide, proinsulin, and Insulinogenic Index. Unlike the Insulinogenic Index, however, the Matsuda ISI was not associated with duration of diabetes.

Thus, while the Insulinogenic Index and Matsuda ISI had similarities in their relations to measures of diabetes control, there were specific differences in their unadjusted associations with cardiovascular risk factors and measures of adiposity.

The Insulinogenic Index, but not the Matsuda ISI, is Associated With Microalbuminuria

In multivariable models, there was an inverse association between microalbuminuria and Insulinogenic Index quartile data (Table 3); subjects with lower β-cell function had higher odds of microalbuminuria. This association remained significant after controlling for history of hypertension, HbA_{1c}, FRS, and cardiac and antihyperglycemic medications. The relationship was moderately attenuated after further adjustment for duration of diabetes (Table 3) as well as BMI (Supplementary Table 2); however, both of these are causally correlated with loss of β-cell function (28), therefore contributing in an expected manner to the observed attenuation. In contrast to the Insulinogenic Index, there was no association between the Matsuda ISI and microalbuminuria in any model (Table 3). Modeling the Insulinogenic Index (inverse normal transformation) or the Matsuda ISI (log-transformed) as continuous traits provided the same pattern of associations with microalbuminuria (Table 3). Likelihood ratio testing in nested models (Supplementary Table 3) and AIC analysis in nonnested models (Supplementary Table 4) suggest an independent association of the Insulinogenic Index with microalbuminuria beyond the Matsuda ISI.

In sensitivity analyses, microalbuminuria modeled as continuous data or an ordinal variable provided similar results (data not shown). In the subsample of participants taking neither insulin nor thiazolidinedione therapy, the association of the Insulinogenic Index with microalbuminuria was consistent with that observed in the full sample (e.g., in fully adjusted model 3: $n = 417$; odds ratio 0.60 [95% CI 0.31–1.20]; $P = 0.15$ for the top versus bottom quartiles of the Insulinogenic Index).

The Matsuda ISI, but not the Insulinogenic Index, is Associated With CAC

In Tobit modeling of CAC data, there was a negative association between the top versus bottom quartiles of the Matsuda ISI and CAC scores in the models adjusted for age, sex, and race. This remained significant after further adjustment for traditional cardiovascular risk factors, including FRS, alcohol use, medications, exercise, hsCRP, microalbuminuria, and duration of diabetes (Table 4). Although the association between the Matsuda ISI and CAC did not weaken substantially after adjusting for individual metabolic syndrome components, it was blunted by inclusion of the binary definition of metabolic syndrome or BMI (e.g., with metabolic syndrome adjustment Tobit ratio −0.61 [95% CI −1.36 to 0.14]; $P = 0.11$) (Supplementary Table 2). This attenuation may arise from causal biological correlations between insulin sensitivity, obesity, and clinical definitions of metabolic syndrome. In the subsample of participants taking neither insulin nor thiazolidinedione therapy, the association of the Matsuda ISI with CAC was consistent with that observed in the full sample (e.g., in fully adjusted model 3: Tobit ratio −0.97 [95% CI −1.87 to −0.06]; $P = 0.037$) for the top versus bottom quartiles of the Matsduda ISI. In contrast to the Matsuda ISI, the Insulinogenic Index was not associated with CAC (Table 4). Modeling the Insulinogenic Index (inverse normal transformation) or the Matsuda ISI (log-transformed) as continuous traits provided results for associations with CAC consistent with those found in the quartile analyses (Table 4). Likelihood ratio testing (Supplementary Table 5) and AIC analysis (Supplementary Table 6) suggest an independent association of the Matsuda ISI with CAC beyond the Insulinogenic Index.

Results were generally similar when CAC data were analyzed by logistic regression for the presence of CAC and by linear regression for the burden of CAC (Supplementary Table 7), although effects were weaker for the log of CAC, perhaps because of the smaller sample.

Comparison of the Insulinogenic Index to HOMA-B and the Matsuda ISI to HOMA-IR

OGTT-derived indices are measures of insulin sensitivity and β-cell function that reflect postprandial pancreatic insulin production and peripheral glucose disposal, respectively, whereas measures based on fasting insulin and glucose, such as the HOMA indices, predominantly capture basal insulin secretion and hepatic glucose production. Because OGTT-derived indices provide a more integrated measure of glucose homeostasis under dynamic settings (16) but are less practical for application in clinical settings, we compared the associations with disease complications of the Insulinogenic Index to HOMA-B and the Matsuda ISI to HOMA-IR. The analysis for HOMA-B excluded participants receiving insulin therapy because these subjects are not typically included in the generation of HOMA-B estimates (25). Although the top quartile of HOMA-B trended toward an inverse association with microalbuminuria, this was not statistically significant (Supplementary Table 8). The top quartile of HOMA-IR similarly trended toward an association with CAC but did not reach statistical significance, unlike the association for the top quartile of the Matsuda ISI (Supplementary Table 9).

Table 2—Characteristics of the study sample across Matsuda ISI quartiles (each *n* = 168)

Variable	Matsuda quartile 1	Matsuda quartile 2	Matsuda quartile 3	Matsuda quartile 4	*P* value*
Matsuda ISI	1.25 (0.95–1.47)	2.10 (1.89–2.28)	3.00 (2.70–3.33)	4.84 (4.23–5.89)	<0.001
Age (years)	59 (54–4)	60 (53–64)	61 (55–65)	60 (53–67)	0.19
Female, %	39.3	27.4	31.0	35.7	0.66
Race, %					0.026
White	66.7	62.5	58.3	54.2	
African American	26.8	31.0	39.9	38.7	
Other	6.6	6.6%	1.8	7.1	
Blood pressure (mmHg)					
Systolic	132 (122–140)	130 (120–142)	130 (121–142)	127 (119–140)	0.15
Diastolic	76 (71–81)	76 (71–82)	76 (71–82)	74 (70–80)	0.25
Total cholesterol (mg/dL)	167 (145–194)	161 (138–180)	162 (144–191)	157 (139–180)	0.063
HDL cholesterol (mg/dL)	40 (34–47)	42 (36–50)	46 (38–55)	49 (40–60)	<0.001
Triglycerides (mg/dL)	141 (102–191)	116 (82–170)	100 (79–148)	87 (65–123)	<0.001
LDL cholesterol (mg/dL)	92 (76–117)	89 (72–108)	89 (74–112)	85 (73–106)	0.036
BMI (kg/m^2)	35.5 (32.5–39.0)	32.9 (29.5–36.4)	31.2 (28.0–36.3)	28.5 (25.7–32.6)	<0.001
Waist circumference (cm)	114 (107–124)	108 (99–117)	104 (97–113)	97 (89–107)	<0.001
Metabolic syndrome (%)	92.9	86.3	79.2	58.3	<0.001
Duration of diabetes (years)	6 (2–11)	6 (3–10)	6 (3–11)	7 (3–15)	0.077
HbA_{1c} (%)	6.7 (6.2–7.8)	6.7 (6.1–7.4)	6.5 (6.0–7.2)	6.3 (5.9–6.9)	<0.001
HbA_{1c} (mmol/mol)	50 (44–62)	50 (43–57)	48 (42–55)	45 (41–52)	<0.001
Glucose (mg/dL)	129 (112–160)	118 (103–140)	112 (96–133)	106 (93–127)	<0.001
Insulin (μIU/mL)	29.5 (24.5–38.1)	17.3 (15.1–21.9)	12.4 (10.8–15.0)	8.4 (6.7–10.6)	<0.001
Insulinogenic Index	0.35 (0.17–0.70)	0.24 (0.14–0.47)	0.25 (0.12–0.45)	0.12 (0.06–0.29)	<0.001
HOMA-IR	9.8 (7.7–13.4)	5.5 (4.4–6.7)	3.5 (3.0–4.2)	2.3 (1.7–2.8)	<0.001
HOMA-B%†	162.3 (119.2–226.0)	101.7 (73.9–156.4)	82.9 (56.3–139.5)	62.6 (39.3–96.2)	<0.001
C-peptide (ng/mL)	4.1 (3.0–4.8)	3.2 (2.4–4.0)	2.8 (2.0–3.5)	2.1 (1.5–2.9)	<0.001
Leptin (ng/mL)	21.5 (14.1–34.3)	16.3 (8.5–25.6)	12.2 (7.8–23.7)	8.7 (4.6–19.8)	<0.001
Proinsulin (pM)	35.3 (26.1–46.7)	25.6 (17.4–32.8)	18.3 (14.0–26.7)	13.5 (10.3–19.0)	<0.001
Current tobacco use, %	7.7	9.5	14.3	11.9	0.11
Current alcohol use, %	44.1	53.6	57.1	52.4	0.10
Exercise, %	56.0	64.9	64.9	66.1	0.19
10-year Framingham risk (%)‡	15 (10–24)	13 (10–20)	13 (8–24)	11 (7–20)	<0.001
C-reactive protein (mg/L)	3.03 (1.29–6.59)	1.74 (0.76–3.86)	1.44 (0.69–4.02)	1.03 (0.58–2.50)	<0.001
Antiplatelet medications, %					
Aspirin	43.5	48.8	39.9	45.2	0.84
Antihypertensive medications, %					
ACE inhibitor	66.7	67.9	66.1	58.3	0.10
β-Blocker	17.3	13.7	17.3	16.1	>0.99
Calcium channel blockers	14.3	16.1	16.7	24.4	0.019
Lipid-lowering medications, %					
Statins	59.5	63.7	55.4	61.3	0.86
Niacin	11.3	10.7	3.6	7.7	0.061
Fibrates	6.0	7.1	4.8	4.2	0.33
Diabetes medications, %					
Metformin	61.9	70.2	71.4	68.5	0.20
Sulfonylureas	27.4	32.1	28.0	35.7	0.19
Thiazolidinediones	9.5	23.8	20.8	27.4	<0.001
Exenatide	8.3	6.0	4.8	4.2	0.090
Sitabliptin	9.5	12.5	10.1	10.1	0.96
Insulin	28.0	26.2	16.7	13.7	<0.001
Serum creatinine (mg/dL)	0.86 (0.71–1.00)	0.89 (0.77–1.02)	0.91 (0.78–1.05)	0.90 (0.79–1.10)	0.005
Microalbumin/urine creatinine ratio (mg/g)	18.6 (11.0–39.8)	16.2 (10.8–33.1)	17.1 (10.8–31.9)	17.1 (10.1–37.5)	0.56
Microalbuminuria, %§	33.9	28.6	26.8	31.6	0.57
CAC score	62 (0–247)	61 (0–302)	34 (0–302)	17 (0–251)	0.13
CAC score >0, %	70.2	70.2	64.9	61.3	0.048

Data are median (interquartile range) unless otherwise indicated. **P* values are from nonparametric tests for trend across ordered groups, an extension of the Wilcoxon rank-sum test. †HOMA-B calculated only for a subsample of participants who were not taking exogenous insulin. ‡Total cholesterol 10-year Framingham risk percentage. §Microalbuminuria defined as a spot urine albumin-to-urine creatinine ratio ≥30 mg/g.

Table 3—Association of the Insulinogenic Index and the Matsuda ISI with microalbuminuria in logistic regression models

	Quartile 2		Quartile 3		Quartile 4		Quartile trend*		Continuous variable	
Microalbuminuria	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Insulinogenic Index										
Model 1	0.76 (0.48–1.20)	0.23	0.77 (0.48–1.21)	0.26	0.54 (0.34–0.88)	0.012	0.49 (0.27–0.89)	0.019	0.80 (0.68–0.95)	0.011
Model 2	0.75 (0.46–1.22)	0.24	0.79 (0.48–1.31)	0.36	0.52 (0.30–0.91)	0.022	0.47 (0.23–0.93)	0.031	0.80 (0.66–0.98)	0.032
Model 3	0.76 (0.46–1.24)	0.27	0.84 (0.51–1.39)	0.50	0.57 (0.33–1.01)	0.055	0.53 (0.26–1.07)	0.078	0.84 (0.68–1.02)	0.084
Matsuda ISI										
Model 1	0.82 (0.51–1.30)	0.39	0.74 (0.46–1.19)	0.22	0.93 (0.59–1.47)	0.75	0.99 (0.87–1.12)	0.87	1.07 (0.81–1.41)	0.65
Model 2	0.87 (0.53–1.42)	0.58	0.87 (0.53–1.44)	0.58	1.20 (0.72–1.99)	0.48	1.07 (0.93–1.22)	0.37	1.28 (0.94–1.75)	0.11
Model 3	0.86 (0.52–1.41)	0.55	0.86 (0.52–1.42)	0.56	1.11 (0.66–1.85)	0.70	1.04 (0.91–1.20)	0.57	1.22 (0.90–1.67)	0.20

Microalbuminuria is defined as a spot urine albumin-to-urine creatinine ratio ≥30 mg/g in each quartile compared with the bottom quartile of the Insulinogenic Index and the Matsuda ISI. In addition, the odds ratios (ORs) for microalbuminuria are presented for the Insulinogenic Index (inverse normal transformation) or the Matsuda ISI (natural log-transformed) modeled as continuous variables. Model 1 included age, race, and sex. Model 2 included Model 1 variables and history of hypertension, HbA_{1c}, total cholesterol-based FRS, and medications. Model 3 included Model 2 variables and duration of diabetes. Medications included statins, niacin, aspirin, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, metformin, sulfonylureas, exenatide, sitagliptin, thiazolidinediones, and insulin. **P* values for trends across quartiles were assessed using an ordinal variable based on the median value of each Insulinogenic Index or Matsuda ISI quartile.

CONCLUSIONS

In our study of patients with type 2 diabetes, we report that the Insulinogenic Index, but not the Matsuda ISI, associated with microalbuminuria after controlling for established cardiovascular risk factors but was not independent of diabetes duration and BMI. Conversely, the Matsuda ISI, but not the Insulinogenic Index, associated with CAC after controlling for multiple cardiovascular risk factors. However, this association was not independent of obesity and metabolic syndrome. Furthermore, relative to fasting-derived HOMA measures, these OGTT-derived dynamic indices of β-cell function and insulin sensitivity seemed to have stronger associations with disease complications.

We found a modest association between impaired insulin sensitivity and burden of subclinical atherosclerosis as measured by CAC. This association has been previously described. We reported that HOMA-IR is associated with coronary atherosclerosis independent of established risk factors in a sample of nondiabetic, predominantly Caucasian subjects with a family history of CVD (12). We extended these findings to subjects with type 2 diabetes who were not taking exogenous insulin (15). In the Multi-Ethnic Study of Atherosclerosis, a study of patients without diabetes or CVD, HOMA-IR was associated with greater subclinical atherosclerosis but was not independent of metabolic syndrome (13). In the San Antonio Heart Study, a large population-based study of Caucasians and Mexican Americans, HOMA-IR was similarly associated with risk of CVD (14), whereas the Insulin Resistance Atherosclerosis Study investigators found an inverse association between insulin sensitivity (measured by frequently sampled intravenous glucose tolerance testing) and carotid wall thickness in Hispanics and non-Hispanic Caucasians (29). Unlike our current work, previous studies were conducted in populations without overt type 2 diabetes.

In this article we extend these prior findings to OGTT-derived indices of insulin sensitivity in a sample of patients with type 2 diabetes. Our results suggest an association between impaired insulin sensitivity and subclinical atherosclerosis that is independent of many potential confounders, including FRS, hsCRP, alcohol use, medications, exercise, diabetes duration, ethnicity, and sex, but it is not necessarily independent of obesity and metabolic syndrome, which may be causally correlated with insulin resistance (30). We also found that, relative to HOMA-IR, the Matsuda ISI had stronger associations with CAC, supporting further examination of such dynamic measures in the study of disease pathophysiology. Higher CAC scores in subjects with the lowest insulin sensitivity independent of many traditional risk factors suggest that insulin resistance or hyperinsulinemia may contribute to subclinical atherosclerosis beyond the atherogenic abnormalities closely associated with type 2 diabetes. The lack of an association between β-cell function and CAC argues against the concept that chronic exposure to hyperglycemia per se drives the increased burden of CAC and atherosclerosis in type 2 diabetes.

There are several potential mechanisms to explain the association between impaired insulin sensitivity and CAC as well as subclinical atherosclerosis. Elevated levels of circulating insulin may have a direct deleterious effect by promoting proliferation of vascular smooth muscle cells (31) and increasing vasoconstriction by vascular endothelial cells (32). Alternatively, hyperinsulinemia may simply be a superior marker of the constellation of abnormalities that characterize metabolic syndrome, including chronic inflammatory signaling, elevated levels of small dense LDL, or a hypercoagulable state. We controlled for established risk factors, which suggests that insulin resistance may confer risk for atherosclerosis independent of many associated confounders, but it is possible that our current conceptualization of cardiovascular risk does not capture all responsible factors.

Table 4—Association of the Insulinogenic Index and the Matsuda ISI with CAC in Tobit regression models

	Quartile 2		Quartile 3		Quartile 4		Quartile trend*		Continuous variable	
CAC	Tobit ratio (95% CI)	*P* value	Tobit ratio (95% CI)	*P* value	Tobit ratio (95% CI)	*P* value	Tobit ratio (95% CI)	*P* value	Tobit ratio (95% CI)	*P* value
Insulinogenic Index										
Model 1	0.35 (−0.34 to 1.04)	0.32	0.20 (−0.49 to 0.89)	0.57	−0.22 (−0.92 to 0.48)	0.54	−0.50 (−1.36 to 0.37)	0.26	−0.07 (−0.32 to 0.18)	0.59
Model 2	0.37 (−0.32 to 1.05)	0.29	0.49 (−0.21 to 1.18)	0.17	0.14 (−0.60 to 0.89)	0.71	−0.04 (−0.96 to 0.88)	0.94	0.10 (−0.17 to 0.37)	0.48
Model 3	0.38 (−0.30 to 1.07)	0.27	0.52 (−0.18 to 1.22)	0.15	0.20 (−0.56 to 0.96)	0.61	0.03 (−0.90 to 0.96)	0.95	0.12 (−0.15 to 0.40)	0.38
Matsuda ISI										
Model 1	−0.23 (−0.93 to 0.46)	0.51	−0.61 (−1.30 to 0.09)	0.087	−0.69 (−1.39 to 0.01)	0.052	−0.19 (−0.38 to −0.01)	0.041	−0.38 (−0.79 to 0.03)	0.071
Model 2	−0.34 (−1.03 to 0.34)	0.33	−0.55 (−1.25 to 0.16)	0.13	−0.75 (−1.47 to −0.02)	0.043	−0.20 (−0.39 to −0.003)	0.047	−0.40 (−0.84 to 0.04)	0.077
Model 3	−0.34 (−1.03 to 0.34)	0.33	−0.55 (−1.25 to 0.16)	0.13	−0.78 (−1.51 to −0.05)	0.035	−0.21 (−0.40 to −0.01)	0.037	−0.42 (−0.86 to 0.03)	0.065

Data are Tobit regression ratios for the associations with CAC score for each quartile compared with the bottom quartile of the Insulinogenic Index or the Matsuda ISI. In addition, Tobit ratios are presented for the Insulinogenic Index (inverse normal transformation) or the Matsuda ISI (natural log–transformed) modeled as continuous variables. Model 1 included age, race, and sex. Model 2 included Model 1 variables and exercise, current alcohol use, high-sensitivity C-reactive protein levels, total cholesterol-based FRS, microalbuminuria, and medications. Model 3 included Model 2 variables and duration of diabetes. Medications included statins, niacin, aspirin, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, metformin, sulfonylureas, exenatide, sitagliptin, thiazolidinediones, and insulin. **P* values for trends across quartiles were assessed using an ordinal variable based on the median value of each Insulinogenic Index or Matsuda ISI quartile.

Although macrovascular complications account for the majority of excess mortality in type 2 diabetes, microvascular complications are a major cause of morbidity. Diabetic nephropathy is the leading cause of renal failure in the United States. It is preceded by microalbuminuria, which typically progresses to proteinuria and overt nephropathy when left untreated. Its pathogenesis is believed to be closely linked to glycemic control because hyperglycemia damages the mesangial cells in the glomerulus (4). The underlying mechanism is incompletely understood but may involve accumulation of sorbitol in cells and subsequent osmotic stress, formation of advanced glycosylated end products, and/or oxidative stress and cellular injury (3). Not surprisingly, since the mechanism of injury seems to be driven by hyperglycemia, tight glycemic control plays a key role in the protection against microvascular complications in type 2 diabetes (8,9,33). Our finding of an association between β-cell function and microalbuminuria is novel and consistent with this understanding of the pathogenesis of microvascular complications (34). Again, we found that the OGTT-derived measure, the Insulinogenic Index, had a stronger association with microalbuminuria than fasting-based HOMA-B.

Previous studies have yielded inconsistent results as to whether there is a relationship between insulin resistance and microalbuminuria. Some studies found an association in type 2 diabetes (5,21,35), while others did not (6,7,36). Prior studies generally used fasting measures of insulin resistance, and associations may differ by ethnicity. We did not find an association between the OGTT-derived Matsuda ISI (or HOMA-IR) and microalbuminuria. These findings suggest that diabetic nephropathy may be more closely associated with the hyperglycemia that accompanies the loss of pancreatic function, rather than hyperinsulinemia, the degree of insulin resistance, or related lipoprotein and inflammatory abnormalities.

Our study has several strengths. To our knowledge, this is the largest study of

OGTT-derived indices in relation to vascular complications in type 2 diabetes. The PDHS used extensive biomarker and imaging phenotyping. Participants were free of confounding clinical CVD and renal disease at recruitment. The study sample included a large representation of African Americans, a historically understudied population. We also acknowledge limitations. In particular, the cross-sectional design cannot determine causation or directionality of relationships. We did not compare surrogate OGTT parameters to gold standard measures derived from clamp studies. However, prior human studies of type 2 diabetes have demonstrated that the Matsuda ISI and Insulinogenic Index are reasonably well correlated with clamp measures of insulin sensitivity (37–39) and β-cell function (37,40), respectively. Another potential limitation is the lack of information about changes in antihyperglycemic medication use over time that may affect disease progression. In addition, our study excluded patients with clinical CVD and elevated serum creatinine in our assessment with subclinical atherosclerosis and microalbuminuria as clinical outcomes. Participants in our OGTT substudy may not completely reflect the full study population. However, because excluded participants had worse diabetic control and more insulin use, their exclusion may have biased our results toward the null rather than accounting for the significant associations we observed. The associations we report are modest and require validation in independent samples. Importantly, based on our findings neither OGTT-derived measures of insulin sensitivity and β-cell function nor fasting HOMA parameters may prove useful for predicting clinical complications beyond consideration of other measurable variables, such as obesity and duration of diabetes, in patients with overt type 2 diabetes. This is particularly a concern for the Insulinogenic Index, which closely associates with diabetes duration. Additional investigation in prospective cohorts and clinical trials is needed to determine whether fasting or dynamic indices of insulin sensitivity and β-cell function have value for the prediction of cardiovascular events and progression to end-stage renal disease.

Although type 2 diabetes is characterized by both a decline in pancreatic β-cell function and impaired insulin sensitivity, we found that dynamic measures of these two aspects of the disease had different associations with microvascular and macrovascular complications.

Funding. This work was supported by a Clinical and Translational Science Award (UL1RR024134) from the National Center for Research Resources and a Diabetes and Endocrine Research Center award (P20-DK 019525), both from the National Institutes of Health (NIH) to the University of Pennsylvania. C.K.M. is a Doris Duke Clinical Research Fellow. R.S. was supported by the University of Pennsylvania Clinical and Translational Science Award K12 KL1RR024132 from the NIH. N.N.M. was supported by grant 5K23HL097151 from the NIH.

Duality of Interest. A.M.M. and C.J.G. are employees of, and hold stock in, Merck Sharp and Dohme Corporation, a subsidiary of Merck and Company, Inc., Whitehouse Station, NJ. M.P.R. received research grants from GlaxoSmithKline and Merck Research Laboratories. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. C.K.M. contributed to data collection, conducted statistical analyses, interpreted findings, and wrote the manuscript. A.M.M. and C.J.G. provided epidemiological expertise, contributed to the study design, interpreted findings, and reviewed and edited the manuscript. T.W.C., K.T., J.F.F., and R.S. contributed to data collection and management. N.N.M. conceived of the project and researched data. A.N.Q. contributed to data collection and analysis and reviewed and edited the manuscript. M.R.R. provided endocrinology expertise during the analysis, interpreted results, and reviewed and edited the manuscript. M.P.R. conceived of the project, conducted statistical analysis, interpreted results, and wrote the manuscript. M.P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in poster form at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

References

1. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130–1139
2. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia 2003;46:3–19
3. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77–82
4. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–1625
5. Hsu CC, Chang HY, Huang MC, et al. Association between insulin resistance and development of microalbuminuria in type 2 diabetes: a prospective cohort study. Diabetes Care 2011;34:982–987
6. Jager A, Kostense PJ, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: the Hoorn Study. Diabetologia 1998;41:694–700
7. Rizvi A, Varasteh B, Chen YD, Reaven GM. Lack of a relationship between urinary albumin excretion rate and insulin resistance in patients with non-insulin-dependent diabetes mellitus. Metabolism 1996;45:1062–1064
8. ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–853
10. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
11. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care 1979;2:120–126
12. 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
13. 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
14. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177–1184

15. Mehta NN, Krishnamoorthy P, Martin SS, et al. Usefulness of insulin resistance estimation and the metabolic syndrome in predicting coronary atherosclerosis in type 2 diabetes mellitus. Am J Cardiol 2011;107: 406–411

16. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470

17. Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. Diabet Med 1994;11:286–292

18. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–2162

19. Rumberger JA, Sheedy PF, Breen JF, Schwartz RS. Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis. J Am Coll Cardiol 1997;29:1542–1548

20. Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571–2576

21. Franciosi M, Pellegrini F, Sacco M, et al.; IGLOO (Impaired Glucose tolerance, and Long-term Outcomes Observational Study) Study Group. Identifying patients at risk for microalbuminuria via interaction of the components of the metabolic syndrome: a cross-sectional analytic study. Clin J Am Soc Nephrol 2007;2:984–991

22. Martin SS, Qasim AN, Mehta NN, et al. Apolipoprotein B but not LDL cholesterol is associated with coronary artery calcification in type 2 diabetic whites. Diabetes 2009;58:1887–1892

23. Vetter ML, Cardillo S, Rickels MR, Iqbal N. Narrative review: effect of bariatric surgery on type 2 diabetes mellitus. Ann Intern Med 2009;150:94–103

24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412–419

25. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495

26. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–1847

27. Reilly MP, Wolfe ML, Localio AR, Rader DJ. Coronary artery calcification and cardiovascular risk factors: impact of the analytic approach. Atherosclerosis 2004; 173:69–78

28. Cederholm J, Eliasson B, Nilsson PM, Weiss L, Gudbjörnsdottir S; Steering Committee of the Swedish National Diabetes Register. Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. Diabetes Res Clin Pract 2005;67:258–266

29. Howard G, O'Leary DH, Zaccaro D, et al.; The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Insulin sensitivity and atherosclerosis. Circulation 1996;93:1809–1817

30. Bonora E, Targher G, Alberiche M, et al. Predictors of insulin sensitivity in Type 2 diabetes mellitus. Diabet Med 2002;19: 535–542

31. Mikhail N, Tuck ML. Insulin and the vasculature. Curr Hypertens Rep 2000;2: 148–153

32. Bakker W, Sipkema P, Stehouwer CD, et al. Protein kinase C θ activation induces insulin-mediated constriction of muscle resistance arteries. Diabetes 2008;57: 706–713

33. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430

34. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009;32(Suppl 2): S151–S156

35. Esteghamati A, Ashraf H, Nakhjavani M, Najafian B, Hamidi S, Abbasi M. Insulin resistance is an independent correlate of increased urine albumin excretion: a cross-sectional study in Iranian Type 2 diabetic patients. Diabet Med 2009;26: 177–181

36. Nielsen S, Schmitz O, Orskov H, Mogensen CE. Similar insulin sensitivity in NIDDM patients with normo- and microalbuminuria. Diabetes Care 1995;18: 834–842

37. Tripathy D, Almgren P, Tuomi T, Groop L. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. Diabetes Care 2004;27:2204–2210

38. Kuo CS, Hwu CM, Chiang SC, et al. Waist circumference predicts insulin resistance in offspring of diabetic patients. Diabetes Nutr Metab 2002;15:101–108

39. Piché ME, Lemieux S, Corneau L, Nadeau A, Bergeron JWS, Weisnagel SJ. Measuring insulin sensitivity in postmenopausal women coveringa range of glucose tolerance: comparison of indices derived from the oral glucose tolerance test with the euglycemic-hyperinsulinemic clamp. Metabolism 2007;56:1159–1166

40. Tura A, Kautzky-Willer A, Pacini G. Insulinogenic indices from insulin and C-peptide: comparison of beta-cell function from OGTT and IVGTT. Diabetes Res Clin Pract 2006;72:298–301