Metabolic Abnormalities Characteristic of Dysmetabolic Syndrome Predict the Development of Transplant Coronary Artery Disease

A Prospective Study

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Background—This study examines the hypothesis that metabolic abnormalities of dysmetabolic syndrome are risk factors for transplant coronary artery disease (TxCAD).

Methods and Results—Sixty-six patients without overt diabetes, 2 to 4 years after surgery, underwent intracoronary ultrasound (ICUS), measurement of plasma glucose and insulin after oral glucose (75 g), and fasting lipid and lipoproteins. TxCAD incidence by angiography or autopsy was prospectively determined during subsequent follow-up (8 years). Coronary artery intimal thickness (IT) and subsequent outcomes were compared in patients stratified as having “high” versus “low” plasma glucose (>8.9 mmol/L) and insulin (>760 pmol/L) 2 hours after glucose challenge; and “abnormal” versus “normal” fasting lipid and lipoprotein concentrations as defined by the National Cholesterol Education Program. Patients with high glucose or insulin concentrations had greater IT: 0.38±0.05 versus 0.22±0.02 mm, P≤0.05, and 0.39±0.05 versus 0.20±0.02 mm, P≤0.01, respectively. Freedom from TxCAD was 56±11% versus 81±6% (P<0.01) in patients with high versus low glucose and 57±10% versus 82±7% (P<0.05) in patients with high versus low insulin. Actuarial survival was 60±12% versus 92±5% (P<0.005) in patients with high versus low glucose and 72±9% versus 88±6% (P<0.05) in patients with high versus low insulin. Triglycerides and VLDL were higher and HDL was lower in patients with IT >0.3 mm than with IT ≤0.3 mm. TxCAD incidence was higher in patients with high plasma TG and VLDL and low HDL.

Conclusions—These data suggest that insulin resistance plays a role in TxCAD. (Circulation. 2001;103:2144-2152.)

Key Words: transplantation ■ atherosclerosis ■ insulin ■ hyperinsulinemia ■ hypertriglyceridemia

We previously reported that hypertriglyceridemia and obesity are independently correlated with transplant atherosclerosis (transplant coronary artery disease, TxCAD) and therefore hypothesized that the metabolic abnormalities characteristic of dysmetabolic syndrome, as described by Reaven and Chen, accelerate TxCAD. To test this hypothesis, we performed cross-sectional and prospective correlations of components of dysmetabolic syndrome with coronary artery intimal thickening (IT) and determined whether any of the metabolic abnormalities predicted the development of clinically significant TxCAD.

Methods

Patients
Sixty-six consecutive heart transplant patients were selected from a cohort of one-year survivors out of 120 patients who had received heart transplants during an interval of 3 years preceding enrollment. Exclusionary criteria included a history of diabetes requiring oral hypoglycemic drug or insulin treatment, refusal of consent, or significant renal dysfunction. All patients were managed with standard immunosuppressive regimens, including prophylactic anti-CD3 orthoclone antibody (OKT3) during the initial 14 days after surgery and maintenance with prednisone (0.1 to 0.5 mg · kg⁻¹ · d⁻¹), azathioprine (2 to 4 mg · kg⁻¹ · d⁻¹), and cyclosporine (2 to 6 mg · kg⁻¹ · d⁻¹). Pretransplantation and posttransplantation clinical characteristics were recorded for each patient. Measurements of plasma glucose, insulin, and lipoprotein concentrations from 40 healthy volunteers were used for comparison to heart transplant patients. The study protocol and written informed consent obtained from all subjects were approved by the Committee for the Protection of Human Subjects in Research at Stanford University Medical Center.

Metabolic Measurements
Glucose and insulin responses to a 75-g oral glucose challenge after a 12-hour overnight fast, plasma triglyceride (TG), cholesterol, VLDL, LDL, and HDL concentrations were measured by standard methods.
Coronary Angiography and Intracoronary Ultrasound

Serial annual angiograms in identical views from each patient were compared side by side by 2 independent experienced angiographers blinded to the clinical, metabolic, or intracoronary ultrasound (ICUS) data. Presence of “any” angiographic disease was selected as the angiographic threshold for abnormality. The actuarial incidence of TxCAD was determined from these annual angiograms and from autopsy data. ICUS imaging of 4 randomly selected sites in the left anterior descending coronary artery was performed as previously described, and IT was determined by planimetry. Measurements from all sites were averaged for each study. IT of >0.3 mm was considered significant on the basis of our previous work demonstrating the prognostic importance of this severity and autopsy observations.

Clinical Events

Clinical events recorded included actuarial survival, TxCAD incidence assessed by annual angiograms and autopsy, death due to TxCAD, and causes of death. To determine whether glucose intolerance, hyperinsulinemia, and/or abnormal plasma concentrations of lipids or lipoproteins predict the subsequent development of TxCAD, the patients were followed up from the time of the glucose tolerance test (GTT) performed between July 1990 and February 1992 until August 1998 or until death, for a mean follow-up of 48.2 ± 10.3 months. No patient was lost to follow-up.

Statistical Analysis

Cross-Sectional Study

Differences between patients with and without TxCAD with respect to the potential confounding covariates were determined. χ² tests were used for comparison of categorical variables and 2-tailed t tests for continuous variables. A probability value of P<0.05 was considered to indicate statistical significance.

Plasma glucose, insulin, lipid, and lipoprotein concentrations, expressed as mean ± SEM, were compared in the 3 study groups: normal control subjects, patients with IT ≤ 0.3 mm, and those with IT >0.3 mm by ANOVA. Coronary artery IT was compared in patients stratified for severity of glucose and insulin concentrations 2 hours after oral glucose challenge by ANOVA. “High” or “low” plasma concentrations of glucose and insulin after glucose load were prospectively defined as values greater or less than the mean ± 1 SEM, respectively. By these criteria, the threshold values for glucose and insulin concentrations were 8.9 mmol/L and 760 pmol/L, respectively.

Average plasma concentrations of lipids and lipoproteins measured annually after heart transplantation were calculated for each patient. ANOVA was used to compare intimal thickness (IT) in patients with abdominal versus those with normal or desirable values for each lipid and lipoprotein, as defined by the National Cholesterol Education Program (NCEP) guidelines: TG ≤ 200 mg/dL, LDL cholesterol (LDL-C) ≤ 130 mg/dL, and HDL-C ≥ 35 mg/dL. Because VLDL-C is not mentioned in the NCEP guidelines and is a value derived from the triglyceride value (1/5), we used a value of 40 mg/dL (1/5 of 200 mg/dL, the triglyceride cutoff). Because plasma lipoprotein and lipid concentrations change after the first year after heart transplantation, annual measurements, distinct from values averaged for the entire follow-up period, were compared in patients with average IT >0.3 mm versus ≤ 0.3 mm.

The correlations of glucose, insulin, lipid, and lipoprotein plasma concentrations with IT were determined by Pearson’s univariate analysis. Parameters found to correlate with IT with a probability of ≤ 0.01 were entered into the Cox multiple regression analysis to determine their independent correlation with IT.

Prospective Study

Clinical outcome variables included TxCAD by angiography and/or autopsy, overall survival, and TxCAD survival defined as freedom from TxCAD death and/or retransplantation for TxCAD. Actuarial incidence of each outcome variable at 5 and 8 years (3 and 5 years after the GTT) was compared in patients stratified by the plasma concentrations of glucose, insulin, lipid, and lipoproteins. Differences in the actuarial incidence of each outcome variable were compared in patients with high versus low plasma concentrations of glucose and insulin (as defined above) and in patients with “normal” versus “abnormal” (as defined above) average plasma lipid and lipoprotein by use of Kaplan-Meier procedures to test for equality of survival curves. A probability of P<0.05 was considered statistically significant. Cox’s proportional hazards model was used to determine which metabolic abnormalities were independently correlated with TxCAD, overall survival, and TxCAD survival.

Results

Cross-Sectional Analyses

TxCAD Diagnosed by ICUS and Angiography

At the annual study coincident with the GTT, the average coronary artery IT for the entire study population was 0.4±0.33 mm. Of the 66 patients studied, 24 had IT >0.3 mm, and in the remaining 42 patients, IT was ≤ 0.3 mm. Mild angiographic evidence of TxCAD (graded as ≤ 30% stenosis in 1 vessel) was present in 4 patients with IT >0.3 mm; the remaining 20 patients had normal coronary angiograms despite IT. None of the 42 patients with IT ≤ 0.3 mm had angiographic evidence of TxCAD. During the subsequent 5-year follow-up period (8 years posttransplantation), the event-free probability of TxCAD by angiography or autopsy was lower in patients whose initial IT was >0.3 mm compared with ≤ 0.3 mm (46±13% versus 82±6%, P<0.005).

Clinical Characteristics as Covariates for IT and Metabolic Abnormalities

Patients with IT >0.3 mm had older donors, higher body mass index, more treated rejection episodes, and lower daily maintenance dose of cyclosporine. No significant differences were found for any of the other covariates.

Compared with patients with low plasma glucose concentration, patients with high plasma glucose concentration 2 hours after glucose load were older at transplantation (51±2 versus 41±2 years, P<0.03) and had more treated rejection episodes (4.6±0.6 versus 3.2±0.3, P<0.03) and higher cumulative pulse-corticosteroid dose (6.3±0.8 versus 4.4±0.6 g prednisone equivalent, P<0.05). Patients stratified according to high versus low plasma concentrations of insulin, TG, VLDL-C, LDL-C, and HDL-C did not differ significantly in any of the baseline and posttransplantation covariates analyzed (data not shown).

Glucose and Insulin Measurements

Plasma glucose and insulin responses before and after a 75-g oral glucose challenge are compared in patients with IT >0.3 mm versus ≤ 0.3 mm (Figure 1A and 1B). Data from 40 healthy volunteers matched for body mass index are presented for comparison. Plasma glucose and insulin concentrations fasting and 1 and 2 hours after glucose challenge were higher in patients than in control subjects. Patients with IT >0.3 mm had higher plasma glucose concentrations after oral glucose challenge than patients with IT ≤ 0.3 mm (P≤0.05) and control subjects (P<0.01). Patients with IT >0.3 mm had higher insulin concentrations than patients with IT ≤ 0.3 mm (P≤0.05) and control subjects (P≤0.01).
Patients with high (>8.9 mmol/L; n=19) plasma glucose concentration 2 hours after oral glucose challenge had higher mean IT than patients with low (≤8.9 mmol/L; n=47) concentrations (0.35±0.05 versus 0.20±0.02 mm, P≤0.05). Patients with high (>760 pmol/L; n=24) plasma insulin concentration after oral glucose challenge had higher mean IT than patients with low (≤760 pmol/L; n=42) concentrations (0.39±0.05 versus 0.21±0.02 mm, P≤0.01).

Average Plasma Lipids and Lipoprotein Concentrations After Transplantation
Patients with coronary artery IT >0.3 mm had higher average concentrations of plasma TG and VLDL-C and lower HDL-C than patients with IT ≤0.3 mm. Heart transplant patients had higher plasma concentrations of TG, total cholesterol, LDL-C, and VLDL-C than normal subjects (P<0.05 to P<0.001; Table 1).

Annual Plasma Lipid and Lipoprotein Concentration Tests After Transplantation
Plasma lipid and lipoprotein concentrations in patients before and annually after transplantation are shown in Figure 2A through 2D (figure for total cholesterol not shown).

Comparisons with pretransplantation measurements. Heart transplant patients with IT >0.3 mm had higher pretransplantation concentrations of TG, total cholesterol, LDL-C, and VLDL-C than patients with IT ≤0.3 mm (P≤0.05). Pretransplantation concentrations of HDL-C did not differ in patients with IT >3 versus ≤3 mm. During the first year after transplantation, TG, total cholesterol, LDL-C, and VLDL-C increased compared with pretransplantation measurements in both patient groups; HDL-C increased in both patient groups, but the increase was significant only in patients with IT ≤0.3 mm. After the first year, patients with IT >0.3 mm had further increases in plasma concentrations of VLDL-C and TG, both of which remained significantly higher than pretransplantation concentrations until year 5 of the follow-up period. In contrast, patients with IT ≤0.3 mm had no significant changes in plasma concentrations of VLDL-C and TG compared with pretransplantation. After the first year, total cholesterol and LDL-C decreased and thereafter were not significantly different from pretransplantation concentrations for either group. The initial increase in plasma HDL-C concentration that occurred in patients with IT ≤0.3 mm persisted throughout the follow-up period; in patients with IT >3 mm, however, there was no significant change in HDL-C compared with pretransplantation concentrations.

Comparisons between patients with IT >0.3 versus ≤0.3 mm. During each of the initial 4 years after heart transplantation, TG and VLDL-C concentrations were higher in patients with IT >0.3 mm than in those with IT ≤0.3 mm. Although total cholesterol and LDL-C showed a trend toward being higher in patients with IT >0.3 mm, the differences were not statistically significant for either. After transplantation, HDL-C was lower in patients with IT >0.3 mm than in patients with IT ≤0.3 mm (P≤0.05 by year 3).

Correlation of Insulin, Glucose, Lipids, and Lipoprotein Concentrations With Coronary Artery IT
IT was significantly correlated with plasma concentrations of glucose and insulin fasting and 2 hours after glucose load (Table 1).
2). IT was significantly correlated with pretransplantation plasma concentrations of TG, total cholesterol, LDL-C, and VLDL-C and with the average and 1-year posttransplantation plasma concentrations of TG and VLDL-C (data not shown). By Cox’s multiple regression analysis, the significant correlates of IT were high plasma concentrations of insulin after glucose loading ($P<0.05$) and high average plasma concentrations of TG ($P<0.01$), VLDL-C ($P<0.05$), body mass index posttransplantation ($P<0.05$), and donor age ($P<0.001$).

Clinical Outcome Analyses

**Plasma Concentrations of Glucose and Insulin on Development of TxCAD, Actuarial Survival, and TxCAD Death/Retransplantation**

**Glucose.** Event-free probability of freedom from TxCAD 5 and 8 years after transplantation (3 and 5 years after GTT) was $70\pm10\%$ and $60\pm11\%$ in patients with high plasma glucose concentrations, compared with $91\pm5\%$ and $81\pm6\%$ in patients with low plasma glucose concentration ($P<0.01$, Figure 3A). Actuarial survival at 5 and 8 years in patients with high plasma glucose concentrations were $90\pm6\%$ and $63\pm12\%$, compared with $100\%$ and $95\pm5\%$ in patients with low plasma glucose concentrations ($P<0.005$, Figure 3B). The event-free probability of freedom from TxCAD death or retransplantation at 5 and 8 years in patients with high plasma glucose concentrations was $90\pm7\%$ at both time points, compared with $100\%$ at both time points in patients with low plasma glucose concentrations ($P<0.05$, Figure 3C).

**Insulin.** Event-free probabilities of freedom from TxCAD 5 and 8 years after transplantation (3 and 5 years after GTT) were $73\pm10\%$ and $67\pm10\%$ in patients with high plasma insulin concentration ($>760$ pmol/L), compared with $85\pm6\%$...
and 75±7% in patients with low plasma insulin concentration 
(P<0.05, Figure 4A). Actuarial survivals at 5 and 8 years in 
patients with high plasma insulin concentrations were 
90±5% and 75±9%, compared with 100% and 90±6% in 
patients with low plasma insulin concentrations (P<0.05, 
Figure 4B). Event-free probability of freedom from TxCAD 
death or retransplantation at 5 and 8 years in patients with 
high plasma insulin concentrations was 86±7% at both time 
points, compared with 100% at both time points in patients 
with low plasma insulin concentrations (P<0.05, Figure 4C).

**Lipids, Lipoproteins, and Development of TxCAD, 
Actuarial Survival, and TxCAD Death/Retransplantation **

**Triglyceride concentrations.** Event-free probability of 
freedom from TxCAD 5 and 8 years after transplantation 
(3 and 5 years after GTT) was 55±14% at both time points 
in patients with high plasma TG concentration, compared 
with 81±6% and 75±7% in patients with low concentrations 
(P#0.05; Figure 5A). Actuarial survivals at 5 and 8 
years in patients with high average plasma triglyceride 
concentrations were 93±7% and 85±10%, respectively, 
compared with 95±3% and 90±10% in patients with low 
plasma TG concentrations (P=NS; Figure 5B). Event-free 
probability of freedom from TxCAD death or retransplant-
atation at 5 and 8 years in patients with high TG was 
93±6% at both time points, compared with 97±2% and 
91±6% at 5 and 8 years, respectively, in patients with low 
TG (P=NS, Figure 5C).

**VLDL-C concentrations.** Event-free probability of free-
dom from TxCAD 5 and 8 years after transplantation (3 
and 5 years after GTT) was 63±11% and 52±15%, re-
spectively, in patients with high plasma VLDL-C con-
centration, compared with 85±2% and 78±5% in patients 
with low concentrations (P=0.005; Figure 6A). Actuarial 
survival at 5 and 8 years in patients with high average 
plasma VLDL-C concentrations was 90±6% at both time 
points, compared with 95±2% and 82±12% in patients 
with low plasma VLDL-C concentrations (P=NS; Figure 
6B). Event-free probability of freedom from TxCAD death 
or retransplantation was similar in the 2 patient groups: 
92±2% at both time points in patients with high VLDL-C 
compared with 95±6% at both time points in patients with 
low VLDL-C (Figure 6C).

**LDL-C.** Event-free probabilities of freedom from TxCAD 5 
and 8 years after transplantation (3 and 5 years after GTT) were 82±6% 
and 76±8% in patients with high plasma LDL-C concentration, 
compared with 74±10% and 62±11% in patients with low LDL-C 
concentrations (P=NS; Figure 7A). Actuarial 5-year and 8-year 
survivals were 100% and 89±6% in patients with high average 
plasma LDL-C concentration, compared with 89±7% and

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**TABLE 2. Correlation* of Insulin, Glucose, Lipids, and Lipoprotein Concentrations With Coronary Artery Intimal Thickening**

<table>
<thead>
<tr>
<th>Variable</th>
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<tr>
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<tr>
<td>Fasting</td>
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<td>0.05</td>
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<td>0.3</td>
<td>0.09</td>
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<td>2 hour</td>
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<td>0.05</td>
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<tr>
<td>Insulin</td>
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<tr>
<td>Fasting</td>
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<td>0.03</td>
</tr>
<tr>
<td>1 hour</td>
<td>0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>2 hour</td>
<td>0.5</td>
<td>0.01</td>
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*Pearson’s correlation.
75±11% in patients with low plasma LDL-C concentration (P=NS; Figure 7B). Event-free probabilities of freedom from cardiac death or retransplantation 5 and 8 years after transplantation were 100% and 94±6% in patients with high LDL-C, compared with 94±5% and 89±7% (P=NS; Figure 7C) in patients with low LDL-C.

HDL-C. Event-free probabilities of freedom from TxCAD 5 and 8 years after transplantation (3 and 5 years after GTT) were 76±9%
and 63±5% in patients with low HDL-C concentrations, compared with 82±4% and 75±5% in patients with high HDL-C concentration (P<0.05; Figure 8A). Actuarial 5-year and 8-year survival was 90±6% in patients with low average plasma HDL-C concentration, compared with 100% and 83±8% (P=NS; Figure 8B) in patients with high plasma HDL-C concentration. Event-free probability of freedom from cardiac death or retransplantation at 5 and 8 years was 90±6% at both time points for patients with low HDL-C, compared with 100% and 93±5% in patients with high HDL-C (P=NS; Figure 8C).
Discussion

This study shows that metabolic markers of insulin resistance, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, high VLDL-C, and low HDL-C are significantly correlated with coronary artery IT in the transplanted heart. These metabolic abnormalities significantly predicted the development of coronary artery stenosis and death during the subsequent 5 years of follow-up. Plasma insulin concentrations after oral glucose challenge were significantly higher in patients with coronary IT ≥0.3 mm, were independently correlated with IT by multivariate analysis, and predicted subsequent development of TxCAD and survival. In contrast, fasting plasma glucose concentration was not significantly different in patients with IT ≥0.3 mm versus ≤0.3 mm and did not predict development of TxCAD. This observation is consistent with previous studies suggesting that diabetes, defined by fasting blood glucose measurements, is not a risk factor for TxCAD. In this study, we excluded patients with a history of overt diabetes requiring pharmacological therapy so as to avoid the variations in glycemia control that might affect the results of these analyses. The GTTs, however, confirmed that even in the absence of fasting hyperglycemia, the majority of patients were hyperinsulinemic.

Prospective studies found that elevated fasting plasma concentrations of insulin are associated with an increased risk of ischemic heart disease in men. Hyperinsulinemia in persons without diabetes may be a marker for a cluster of metabolic abnormalities, including impaired insulin-mediated glucose uptake, visceral obesity, dyslipidemia, and hypertension. Our results are consistent with this concept, because we observed that in addition to hyperinsulinemia and hyperglycemia, obesity was also significantly correlated with coronary artery IT.

It is unknown whether the relationship between hyperinsulinemia and ischemic heart disease is independent of related risk factors, such as hyperlipidemia. Insulin resistance impedes the removal of triglycerides from VLDL in the circulation, resulting in hypertriglyceridemia and high VLDL concentrations, as we observed in transplant patients with the greatest coronary artery IT. Furthermore, the expanded VLDL pool increases the transfer of cholesterol out of HDL and probably out of LDL to VLDL. This in turn leads to low levels of HDL-C and the formation of small cholesterol-depleted LDL. These small dense LDL particles are rich in triglycerides but contain relatively little cholesterol and are not readily cleared by the physiological LDL receptor. On the contrary, they readily undergo oxidative modification and become highly atherogenic. Thus, it has been suggested that the risk associated with hyperinsulinemia as a marker of insulin resistance is largely explained by the lipid abnormalities. The results of the present study suggest that both insulin resistance and the associated lipid and lipoprotein abnormalities are involved in the process of TxCAD. The cross-sectional study indicated plasma insulin concentrations, triglycerides, VLDL-C, and low HDL-C to be independent predictors of coronary artery IT. In the prospective study, hyperinsulinemia and hypertriglyceridemia, high VLDL, and low HDL predicted the development of TxCAD and survival. It is likely that these abnormalities act in concert to drive the atherosclerotic process.

The mechanisms leading to the profound metabolic derangement we described in heart transplant patients are
poorly defined but are most likely related to the immunosuppressive drugs. Both corticosteroids and cyclosporine have been implicated in glucose intolerance and dyslipidemia. The majority of evidence, however, suggests that corticosteroids are the predominant mediators of lipid abnormalities, because hyperlipidemia improves when patients are maintained in steroid-free regimens, in parallel with a decreased frequency of TxCAD. The metabolic derangement induced by corticosteroids is thought to be mediated by reduced lipoprotein lipase activity, resulting in impaired breakdown of VLDL, increased hepatic secretion of VLDL, and overproduction of TG by the liver. Although corticosteroids appear to be a major predisposing factor for the metabolic abnormalities associated with TxCAD, it is important to note that HDL is raised by corticosteroids. This potential beneficial effect of corticosteroids was not observed in this study, suggesting a dominance of other factors that predispose to HDL lowering, including cyclosporine. Irrespective of which immunosuppressive agent contributes most to hyperlipidemia after heart transplantation, the results of prospective randomized trials showing that prophylactic treatment with the HMG-CoA reductase inhibitors decreases the incidence of TxCAD suggest that the cholesterol hypothesis may also be true for coronary atherosclerosis in the transplanted heart.

**Study Limitations**

The cross-sectional design of this study imposes important limitations with respect to patient selection, because the entry criteria were based on selection of surviving patients presenting for annual evaluation. The exclusion of patients who died before the study may have seriously biased the sample, underrepresenting patients with early and rapidly progressive TxCAD. Second, although patients were followed up prospectively to determine whether each metabolic component of dysmetabolic syndrome predicted TxCAD outcome, the study was not sufficiently powered to assess these end points and multiple covariates. Third, we did not evaluate the role of platelet aggregation, another important component of dysmetabolic syndrome. Proof of a causal role of insulin resistance in the pathophysiology of TxCAD will require a randomized clinical trial of agents that enhance insulin-stimulated glucose uptake.

**References**


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