Diabetes and Occult Coronary Artery Disease

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Severe 3-vessel CAD in a Diabetic Patient and Dyspnea attributed to COPD
Diabetes and CAD: A Terrible Combination

- Frequently silent ischemia (Diabetes Care 2004;27:1954-61)
- Initial manifestation could be multi-vessel CAD or “end-stage” (Am J Cardiol 2000;86:897-902)
Diabetes and CAD: A Terrible Combination

- Poor coronary collateral development (Circulation 1999;99:2239-2242)
- High risk with both angioplasty and CABG versus non-diabetic patients (Am J Cardiol 1994;74:334-339; Circulation 1996;94:1818-1825)
Likely Explanation:

We are NOT detecting the occult CAD in diabetic patients!
Prolonged Latent Period of Undiagnosed DM

- Prevalence of retinopathy used to estimate the latent period of undiagnosed DM and its implication.

- “Onset of NIDDM occurs at least 4-7 years before clinical diagnosis.”

- “Because other data indicate that diabetes may be present for 5 years before retinopathy becomes evident, onset of NIDDM may occur 9-12 years before its clinical diagnosis.”

Adverse Effects of Hyperglycemia

- Inflammation
- Endothelial dysfunction
- Activated platelet activity
- Deranged nitric oxide metabolism

Am J Cardiol 2006;98:842-856
Dibetics have diffuse atherosclerosis with large plaque burden.

- IVUS evaluation of plaque burden in REVERSAL Study
- In multivariate analysis, diabetes, male gender, and a history of a prior interventional procedure were strong predictors of increased atheroma volume.
- Although diabetics had increased disease burden by IVUS measures compared with non-diabetics, angiographic stenosis severity was not different.
- Most likely a major cause of difficulty with detection and revascularization

JACC 2006;47:1967-75
Relevant Questions

- Will aggressive screening identify those diabetic patients with occult CAD?

- WILL IDENTIFICATION AND REVASCULARIZATION OF DIABETIC PATIENTS WITH OCCULT CAD IMPROVE SURVIVAL?
**DIAD Study**

- Detection of Ischemia in Asymptomatic Diabetics
- 1,123 patients with type 2 diabetes, aged 50-75 years, with no known or suspected coronary artery disease
- Randomly assigned to either stress testing and 5-year clinical follow-up or to follow-up only
- CAD/silent ischemia assessed by adenosine technitium-99m sestamibi single-photon emission-computed tomography myocardial perfusion imaging

*Diabetes Care 2004;27:1954-1961*
**DIAD Study Results**

- 60% had two or more ADA screening risk factors.
- Only 50% were capable of performing low-level exercise in conjunction with adenosine infusion.
- 22% had silent ischemia with 6% having moderate to large perfusion defect.
- In multivariate logistic regression, the lowest quartile of heart rate ratios during the Valsalva maneuver (cardiac autonomic dysfunction), male sex, and diabetes duration were independent predictors of moderate or large perfusion abnormalities.

*Diabetes Care* 2004;27:1954-1961

*CAVEAT: “Balanced Ischemia”*
Detection of Coronary Artery Disease in Asymptomatic Patients With Type 2 Diabetes Mellitus

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OBJECTIVES We sought to verify the effectiveness of current American Diabetes Association screening guidelines in identifying asymptomatic patients with coronary artery disease (CAD) in type 2 diabetes mellitus (DM2).

BACKGROUND In DM2 patients, CAD generally is detected in an advanced stage with an extensive atherosclerosis and poor outcome, whereas CAD in an asymptomatic stage is commonly missed.

METHODS This study included 1,899 asymptomatic DM2 patients (age ≤60 years). Of these, 1,121 had ≥2 associated risk factors (RFs), group A, and the remaining 778 had ≤1 RF, group B, for CAD. All patients underwent dipyridamole myocardial contrast echocardiography (MCE), and in those with myocardial perfusion defects, the anatomy of coronary vessels was analyzed by selective coronary angiography.

RESULTS In the two study groups, the prevalence of abnormal MCE (59.4% vs. 60%, p = 0.96) and of a significant CAD (64.6% vs. 65.5%, p = 0.92) was similar, irrespective of RF profile. But coronary anatomy differed: group B had a lower prevalence of three-vessel disease (7.6% vs. 33.3%, p < 0.001), of diffuse disease (18.0% vs. 54.9%, p < 0.001), and of vessel occlusion (3.8% vs. 31.2%, p < 0.001), whereas one-vessel disease was more frequent (70.6% vs. 46.3%, p < 0.001). Coronary anatomy did not allow any revascularization procedure in 45% of group A patients.

CONCLUSIONS An “aggressive” diagnostic approach, requiring coronary angiography in asymptomatic DM2 patients with ≥1 associated RF for CAD and abnormal MCE, identified patients with a subclinical CAD characterized by a more favorable angiographic anatomy. The criterion of ≥2 RFs did not help to identify asymptomatic patients with a higher prevalence of CAD and is only related to a more severe CAD with unfavorable coronary anatomy. (J Am Coll Cardiol 2006;47:65–71) © 2006 by the American College of Cardiology Foundation
Prevalence of CAD (60% in both groups!)

JACC 2006;47:65-71
Prevalence of “Diffuse” CAD

Group A
(≥2 risk factors)
54.9%
31.2%

Group B
(≤1 risk factor)
18.8%
3.5%

JACC 2006;47:65-71
**Complete Revascularization**

- **Group A** (≥2 risk factors):
  - 41.6%
  - **Revasc**

- **Group B** (≤1 risk factor):
  - 11%
  - **Revasc**

**NSR = Anatomy not suitable for revascularization**

*JACC 2006;47:65-71*
Resolved Issue

- Will aggressive screening identify those diabetic patients with occult CAD? **YES!**

- The earlier the screening, the greater the likelihood for detection of less complex coronary artery disease more amenable to revascularization.
Improved Survival in Asymptomatic Diabetic Patients with High-Risk SPECT Imaging Treated with CABG

- 826 asymptomatic diabetics without known CAD, who had abnormal SPECT

- Revascularization was independently associated with improved survival in patients with high-risk scans, with 5-year survival after CABG of 85%, after PCI of 72%, and with medical therapy of 67% (p=0.02).

- There was no survival advantage by treatment for patients with less severe SPECT abnormalities.

*Circulation 2005;112(Suppl I):I-311-I-316*
Candidates for SPECT Screening

- Among 1,427 asymptomatic diabetic patients without known CAD, an abnormal stress SPECT imaging scan was present in 58% and a high-risk scan in 18%.

- Multivariate analysis demonstrated Q waves on EKG and peripheral arterial disease as the most significant predictors of high-risk SPECT imaging result.

- Annual mortality rates by SPECT imaging scans were high-risk 5.9%, intermediate-risk 5%, and low-risk 3.6% (p<0.001).

*JACC 2005;45:43-9*
Importance of Coronary Artery Calcification and Plasma Osteoprotegerin Level

OBJECTIVES
This study sought to prospectively evaluate the relationship between plasma osteoprotegerin (OPG), inflammatory biomarkers (high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6]), coronary artery calcification (CAC), and cardiovascular events in patients with type 2 diabetes.

BACKGROUND
Arterial calcification is a prominent feature of atherosclerosis and is associated with an increased risk of cardiovascular events. Osteoprotegerin is a cytokine that has recently been implicated in the regulation of vascular calcification.

METHODS
A total of 510 type 2 diabetic patients (53 ± 8 years; 61% male) free of symptoms of cardiovascular disease were evaluated by CAC imaging. Risk factors, hs-CRP, IL-6, and OPG levels were measured. Patients were followed up for cardiovascular events (cardiac death, myocardial infarction, acute coronary syndrome, late revascularization, and nonhemorrhagic stroke).

RESULTS
Significant CAC (>10 Agatston units) was seen in 236 patients (46.3%); OPG was significantly elevated in patients with increased CAC. In multivariable analyses, OPG retained a strong association with elevated CAC scores after adjustment for age, gender, and other risk factors (odds ratio = 2.84, 95% confidence interval 2.2 to 3.67; p < 0.01). Sixteen cardiovascular events occurred during a mean follow-up of 18 ± 5 months. The waist-to-hip ratio, United Kingdom Prospective Diabetes Study (UKPDS) risk score, OPG level, and CAC score were significant predictors of time to cardiovascular events in a univariate Cox proportional hazards model. In the multivariate model, the CAC score was the only independent predictor of adverse events. Levels of hs-CRP and IL-6 were related to neither the extent of CAC nor short-term events.

CONCLUSIONS
A high proportion of asymptomatic diabetic patients have significant subclinical atherosclerosis. Of the biomarkers studied, only OPG predicted both subclinical disease and near-term cardiovascular events. Therefore, measurement of OPG merits further investigation as a simple test for identifying high-risk type 2 diabetic patients. (J Am Coll Cardiol 2006;47:1850–7)
In asymptomatic patients with NIDDM, only osteoprotegerin (rather than high sensitivity-CRP or interleukin-6 levels), predicted both subclinical coronary artery disease and short-term cardiovascular events.

Could this biomarker be a simple test to identify high-risk type 2 diabetic patients with asymptomatic CAD?

*JACC 2006;47:1850-7*
Figure 3. Event-free survival at 18 ± 5 months by the Cox proportional hazards model according to the extent of coronary calcification level (A) and plasma osteoprotegerin (OPG) level (B), respectively. RR = relative risk ratio.
Multi-Slice CT for Screening
Important Questions

- Will aggressive screening identify those diabetic patients with occult CAD? **YES!**
- Will revascularization regardless of the symptom status in these diabetic patients improve survival? **Probably.**
Conclusions

- Routine screening of diabetic patients regardless of symptom status should uncover a large percentage of patients with occult CAD.

- Both aggressive risk factor modification and revascularization should improve the poor prognosis in diabetic population.

- It remains to be determined whether percutaneous intervention could rival the benefits of bypass surgery.

- New non-invasive imaging modalities and novel biomarkers may further aid in the early detection of occult CAD in diabetics.