EDITORIAL
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Early Detection of Asymptomatic Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus

Ho-Joong Youn

Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Korea

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Coronary artery disease (CAD) accounts for a large fraction of the morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). T2DM is recognized as a CAD risk factor [1]. Patients with T2DM are also at greater risk for silent ischemia and infarction, with a higher prevalence of multi-vessel CAD. Delayed identification of CAD in patients with T2DM unquestionably worsens their prognoses. Thus, there is a clear need to identify patients with T2DM who are at risk for cardiovascular events before the onset of symptoms, although the utility of screening patients with T2DM for asymptomatic coronary atherosclerosis remains debatable.

About 11 years ago, the American Diabetes Association suggested a risk factor-guided screening approach (*e.g.*, considering age, gender, hypertension, and dyslipidemia) for early detection of CAD in patients with symptomatic and asymptomatic T2DM [2]. However, subsequent studies have shown that the traditional risk factors do not accurately predict the risk for cardiovascular events in T2DM patients [3]. This provides a rationale for an aggressive screening approach for CAD in asymptomatic patients with T2DM, almost independent of other risk factors. Nevertheless, there is no uniform policy regarding CAD screening in patients with T2DM, reflecting the statistical challenges of screening patients at low risk and the decisions that should be made from the resulting data. Generally, a resting electrocardiogram (ECG) and resting echocardiography are incapable of detecting asymptomatic CAD. Indeed, stress tests are needed for the early detection of CAD.

The exercise ECG test is a popular stress test that has good accessibility and relatively low-cost. An exercise ECG test is an established method in subjects with known CAD, but its diagnostic accuracy is low in individuals with early atherosclerosis. Furthermore, few data exist on the relationship between exercise ECG test results and CAD risk in persons with T2DM, and most studies have involved small samples. Recently, William et al. [4] studied 2854 men with documented T2DM and showed that equivocal and abnormal exercise ECG responses in diabetic patients were associated with higher risk for all-cause cardiovascular disease and CAD mortality. William et al. [4] strongly recommended performing an exercise ECG test in patients who have had T2DM for ≥10 years and who have any family history of cardiovascular disease. Although recent studies regarding the exercise ECG test have shown good results for the early detection of CAD in diabetic patients, its value in diabetic patients is limited, because its low sensitivity requires a workload that is difficult to achieve in diabetic patients owing to comorbidities such as peripheral neuropathy, peripheral arterial diseases, and poor physical fitness.

There is abundant evidence that carotid intima-media thickness (c-IMT) is a surrogate marker of subclinical CAD in both the general population and in patients with T2DM. Wagenknecht et al. [5] showed that the progression of c-IMT was 25% greater in diabetic subjects than in non-diabetic subjects. However, the measurement of c-IMT is an operator-dependent technique, making intra- and inter-observer variability an issue. Furthermore, there are no widely accepted age- and gender-adjusted reference ranges for c-IMT.

Newer imaging methods such as myocardial perfusion scintigraphy using single-photon emission computed tomography (SPECT) and cardiac computed tomography angiography (CCTA) allow direct quantification of the

Correspondence to Ho-Joong Youn, M.D., Ph.D.
Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea College of Medicine, 62 Yoido-dong, Youngdungpo-gu, St. Mary's Hospital, Seoul 150-713, Korea
Tel: 82-2-3779-1325, Fax: 82-2-3779-1374, E-mail: younhj@catholic.ac.kr

coronary atherosclerotic burden and can predict the risk for cardiac events. Thus, these imaging tools are available for the early detection of coronary atherosclerosis. Myocardial SPECT with pharmacological stress has proved to be valuable in detecting silent CAD in asymptomatic diabetic patients, and its diagnostic accuracy is fairly high [6]. Although SPECT is more expensive than an exercise ECG test, its higher accuracy and lower non-diagnostic rate may make it a more cost-effective initial screening test. This functional imaging technique, however, does not always correlate with the anatomic situation and shows suboptimal sensitivity and specificity. Additionally, this technique cannot show the unstable plaque responsible for acute coronary syndrome. Recently, in a randomized controlled study, cardiac event rates were low and were not significantly reduced by myocardial SPECT screening for myocardial ischemia [7].

Non-invasive anatomic imaging such as CCTA with coronary artery calcium scoring can provide direct visualization of the coronary artery and has emerged as an alternative modality for the detection of occult CAD. However, most individuals with CAD have a plaque burden composition characterized by a combination of different types of plaque. Importantly, the role of coronary imaging in diabetic patients is not to document the presence of coronary atherosclerosis, but to identify those patients with more extensive disease who may benefit from further testing to reveal significant inducible myocardial ischemia [8]. Eventually, better imaging techniques will be needed to assess both the degree of plaque burden (soft and calcified) and the extent of vulnerable plaques.

The combined use of anatomic atherosclerosis imaging and functional imaging is emerging as a complementary strategy [9], but the clinical application and cost-effectiveness of such an approach must be evaluated in prospective trials. For a screening test to be useful, the following conditions must be satisfied [10]: (i) it should be commonly available and relatively low-cost (cardiac SPECT and CCTA are expensive diagnostic tools), with a cost-effectiveness analysis of the screening process; (ii) it should have high positive and negative predictive values (the ability of myocardial SPECT to identify low-risk diabetic patients may not be as accurate, and the true prevalence of CAD in asymptomatic T2DM is unknown); and (iii) it should dictate decisions in clinical management that change the natural history of the disease (unfortunately, there is no randomized controlled study comparing treatment strategies in asymptomatic diabetic patients).

Based on their well-designed clinical study, Yoo et al. recommended the use of an exercise ECG test for the early detection of asymptomatic CAD in patients who have had T2DM for ≥10 years and who have a family history of cardiovascular disease. From a clinical view point, this recommendation is meaningful because some factors do contribute to the early detection of asymptomatic CAD in T2DM. However, this study had some limitations. First, the number of study subjects was too small to obtain statistical significance. Second, the exercise ECG test has limited value in detecting early CAD, because of its low sensitivity. Third, the exercise ECG test may not be applicable in T2DM patients with autonomic dysfunction and/or physical unfitness. Thus, the clinical usefulness of an exercise ECG test as a tool for the early detection of asymptomatic CAD in T2DM should be cautiously interpreted.

In conclusion, there is still no convincing evidence that screening programs to prevent cardiovascular events in patients with T2DM are cost-effective. Despite many uncertainties, however, we have highlighted some key points underlying the rationale for screening this high-risk population for heart disease. The detection of silent CAD in patients with T2DM will become an even greater public health issue in the future, as the number of people with T2DM increases. There are sound arguments on both sides of this issue, and the controversy can only be resolved by gathering more evidence from randomized controlled clinical trials. **(Korean J Intern Med 2009;24:180-182)**

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