Clinical case

The role of new cardiovascular risk factors in the assessment of silent coronary artery disease in diabetic patients: when attending guidelines may not be enough

Summary
Silent coronary artery disease (CAD) is common among diabetic patients. The presence of silent CAD is considered a powerful predictor of future cardiovascular events and early death, particularly in diabetic patients. Early identification of diabetic patients with silent CAD can permit their early treatment and consequent improvement of the cardiovascular prognosis. Recent studies showed new powerful predictors of silent CAD in diabetic patients. These predictors are: lipoprotein(a), homocysteine, insulin-resistance and, above all, erectile dysfunction. The case suggests that these new predictors could be effectively used in clinical practice, in order to early identify diabetic patients with silent CAD.

Gazzaruso C, De Amici E. The role of cardiovascular risk factors in the assessment of silent coronary artery disease in diabetic patients: when attending guidelines may not be enough. Trends Med 2006; 6(3):257-260.

Carmine Gazzaruso, Emanuela De Amici
IRCCS Fondazione Maugeri Pavia

A 51 years old man attended our outpatients diabetes clinic on september 2001 because of the recent onset of type 2 diabetes mellitus. He had fasting glycemia: 199 mg/dl, hemoblobin A1c: 9.5%, total cholesterol: 253 mg/dl, HDL: 39 mg/dl, triglycerides: 257 mg/dl. LDL was calculated according to the Friedewald formula and was 163 mg/dl. Systolic blood pressure was 165 mmHg and diastolic blood pressure 95 mmHg. These values of blood pressure were similar to those measured in several previous occasions. His waist circumference was 116 cm. According to the National Cholesterol Education Program (NCEP) criteria, the patient had metabolic syndrome. A hypocaloric and hyposodic diet was prescribed. Mild to moderate physical activity was suggested. Therapy with metformin (1500 mg/die) was started.

To better stratify his global cardiovascular risk and to verify the presence of possible complications, the patient was required to perform several laboratory and instrumental checks. Some of the so-called new cardiovascular risk factors, such as homocysteine, Lipoprotein(a) and Homeostasis Model Insulin-resistance Assessment (HOMA) index were also suggested. As any diabetic male, the patient was screened for the presence of erectile dysfunction

Carmine Gazzaruso, MD PhD
Via Aselli 5
27100 Pavia
E-mail: c.gazzaruso@tele2.it

(ED) by the validated self-administered questionnaire International Index Erectile Function-5 (IIEF-5), that is a 5-item simple questionnaire to verify the presence and the degree of ED. The patient reached a score of 12. So we diagnosed the presence of ED. We informed the patient that ED can be treated effectively with phosphodiesterase-5 inhibitors and that these drugs can be prescribed as soon as the global risk for cardiovascular disease is assessed. Nevertheless, the patient stated that at the moment he did not want to be treated for ED. Three months after, he had fasting glycemia: 151 mg/dl, hemoblobin A1c: 8.3%, total cholesterol: 241 mg/dl, HDL: 39 mg/dl, triglycerides: 221 mg/dl. LDL was 158 mg/dl. Systolic blood pressure was 160 mmHg and diastolic blood pressure 90 mmHg. His waist circumference was 115 cm. These data suggested an improvement in metabolic control. Lipids and hypertension were improved, but their values were higher than those recommended by scientific associations. Indeed in diabetic patients NCEP guidelines recommend LDL levels lower than 100 mg/dl. In addition American Diabetes Association (ADA) guidelines recommend blood pressure values lower than 130/80 mmHg. The patient had additional cardiovascular risk factors: microalbuminuria (34 mg/die), family history of CAD, smoking habits, high Lipoprotein (a) levels (31,1 mg/dl), marked insulin-resistance (HOMA index: 6.7). Interestingly, basal ECG showed the presence of abnormal T-waves and a Q-wave on DIII. Nevertheless, Rose questionnaire to assess the history of cardiovascular disease was negative. Fluvastatin (80 mg/die) and valsartan (80 mg/die) were prescribed. Dosage of metformin was increased (2550 mg/die).

According to the ADA consensus conference on the diagnosis of silent coronary heart disease (CAD) in diabetic patients, an exercise ECG testing was performed, which was negative for stress- induced ischemia. Echocardiography showed normal features. So, according to the current guidelines, no additional testing was suggested by the cardiologist in order to detect the presence of silent CAD. Anyway, considering the elevated cardiovascular risk of the patient, aspirin therapy was started.

One year later, the patient referred to cardiology outpatient unit bacause of new onset dyspnea (with lung crackles) and edema of the limbs; he recently had had flu-like syndrome (cough and mild fever), treated by the family doctor with antibiotic therapy. Basal ECG featured inferior myocardial ischemia. The patient was admitted to cardiology unit. Echocardiography showed diffused hypocinesia with globally depressed systolic function (EF: 45%). Considering the relatively recent negative exercise ECG testing, symptoms and signs of the patient were first considered as features of metabolic hypokinetic cardiomyopathy. Clinical conditions gradually improved. A few months later, a control echocardiography displaied normal systolic function without any abnormal cynetic pattern. Anyway, considering the high global cardiovascular risk of the patient, a myocardial scintigraphy was performed; it revealed mild-to-severe grade inducible myocardial ischemia, involving the basal area. The patient was consequently addressed to coronarography, which showed bivasal coronary stenosis, successfully treated with percutaneous transluminal coronary angioplasty (PTCA) and paclitaxel-eluting stent. After PTCA the patient did not complain either angina or dyspnea any more. No more edema of the limbs was reported. Echocardiography did not show abnormal findings, with improved systolic function (EF: 53%). A control myocardial scintigraphy, which was performed after dipiridamol-induced stress, did not exhibit abnormal perfusion and global findings were significantly improved compared with those before PTCA.

Silent CAD is an important life-threatening condition that is particularly common in diabetic patients[1]. Asymptomatic CAD is a strong predictor of future coronary events and early death, especially in diabetic patients[1]. The early identification and treatment of subjects with silent CAD is very important since in this way it is possible to improve greatly their prognosis[1]. ADA recommends screening for silent CAD in diabetic patients either with complications or ECG abnormalities at rest or in the presence of two or more cardiovascular risk factors among those listed in Table 1. Nevertheless, the most recent American Heart Association guidelines are much more conservative in their recommendations for CAD screening in diabetes. Indeed they conclude that screening is not recommended on a routine basis at this time because it would not change management or lead to improvement in ou-

Table 1. Risk factors to be considered for a possible indication for exercise testing in uncomplicated diabetic patients according to the American Diabetes Association guidelines

- Total cholesterol >240 mg/dl, LDL >160 mg/dl, or HDL <35 mg/dl
- Blood pressure >140/90 mmHg
- Smoking
- Family history for CAD
- Micro or macroalbuminuria

tcomes[1]. However, the Adult Treatment Panel III of the National Cholesterol Education Program has recently suggested that in people at very high cardiovascular risk, such as diabetic patients with CAD, an LDL goal of <70 mg/dl is a reasonable clinical strategy[1]. In high risk persons, such as diabetic patients without evidence of CAD, the recommended LDL goal is <100 mg/dl[1]. The identification of subjects with asymptomatic CAD may help to decide the therapeutic option[1].

Increasing evidence is accumulating about the importance of new cardiovascular risk factors in the identification of people at elevated risk for silent CAD. Indeed, we showed that Lipoprotein(a) levels, homocysteine levels and apo(a) phenotypes can be reliable markers of asymptomatic CAD has been shown in diabetic patients[1]. Moreover, in these patients a significant association of ED and HOMA index with asymptomatic CAD has been recently reported[2,3]. ED has been even proposed as an "atypical" sign of silent CAD[4]. Taken together, the above studies seems to show that "new" cardiovascular risk markers, such as genetic risk factors, insulin-resistance and ED may be included into a "global risk panel" in order to better identify subjects to screen for the presence of silence CAD. In addition, among these new cardiovascular risk factors, the presence of ED should be regarded as an atypical sign of silent CAD, especially in diabetic patients with additional traditional cardiovascular risk factors.

In our diabetic patient silent CAD was not diagnosed at the moment of the screening for CAD, but when symptoms occurred. All guidelines have been followed; nonetheless silent CAD was not identified by using usual first-line screening testing. On the basis of the recent evidence of the literature, the present case suggests the importance to the so-called "new" risk factors in the assessment of global cardiovascular risk in diabetic patients. Indeed, in our patient three "non traditional" risk factors were present (high Lipoprotein(a) levels, ED and high HOMA index) in addition to other cardiovascular risk factors reported in Table 1. Moreover, abnormalities of resting ECG were present. Therefore the risk for silent CAD in our patient appeared to be extremely high. In particular the presence of ED strongly predicted the presence of asymptomatic CAD. This suggests that in selected diabetic patients who have both "new" and traditional risk factors, especially when show abnormal basal ECG and have ED, an exercise- ECG-testing should not be considered sufficient to detect silent CAD. Exercise ECG is the most widely used screening approach in general practice. Although a negative exercise testing at high workload provides reassurance that severe CAD is not present, standard exercise testing has limitations, including a relatively low sensitivity for the detection of moderate CAD. Therefore, cardiac assessment should require further testing in selected diabetic patients at very high risk of silent CAD. Important additional information can be given by stress myocardial perfusion imaging or stress echocardiography, that are able to increase sensitivity and specificity of exercise ECG. This approach may permit the identification of a higher proportion of subjects with silent CAD and their earlier treatment with possible improvement of cardiac prognosis. TiM

References

1. **Gazzaruso C.** Erectile Dysfunction and silent myocardial ischemia. In: Harrison's Principles of Internal Medicine, 16th Edition online, McGraw Hill 2005.
2. **Gazzaruso C, Giordanetti S, De Amici E, *et al.***

Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. Circulation 2004; 110:22-26.
3. **Gazzaruso C, Solerte SB, De Amici E, *et al*.** Association of the Metabolic Syndrome and Insulin-Resistance with Silent Myocardial Ischemia in Patients with Type 2 Diabetes Mellitus. Am J Cardiol 2006; 97:236-239.
4. **Stern S.** Symptoms other than chest pain may be important in the diagnosis of "silent ischemia", or "the sounds of silence". Circulation 2005; 111:e435-e437.