Endocrine (2011) 40:273–279
DOI 10.1007/s12020-011-9523-9

ORIGINAL ARTICLE

Erectile dysfunction can improve the effectiveness of the current guidelines for the screening for asymptomatic coronary artery disease in diabetes

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Received: 25 July 2011 / Accepted: 1 August 2011 / Published online: 23 August 2011

Abstract About 40% of diabetic patients with asymptomatic coronary artery disease (CAD) are missed on the basis of the current screening guidelines. Erectile Dysfunction (ED) is a powerful marker of asymptomatic CAD. Aim of the study is to evaluate whether ED can improve the effectiveness of the current guidelines for the screening of CAD in diabetes. From among 299 consecutive men with newly diagnosed type 2 diabetes without any apparent vascular complication, 293 (mean age 56.6 ± 5.9 years) were enrolled. Among them, 219 did not have myocardial ischemia (NO CAD group) and 74 men had a coronary stenosis angiographically proven (CAD group). Five risk factors (RFs) of the current screening guidelines (hypertension, dyslipidemia, family history for CAD, smoking e micro/macroalbuminuria) and ED were assessed. ED was significantly more prevalent in the CAD than in the NO CAD group (37.8 versus 15.1%; $P < 0.001$) and was a predictor of asymptomatic CAD (OR: 4.4; 95%CI: 2.1–9.0; $P < 0.001$). If ED is added to the list of RFs, it can increase the sensitivity of the current guidelines from 62 to 89%, without a significant variation in specificity (from 60 to 57%). The negative predictive value can increase from 82 to 94%. ED can reduce from 37.84 to 10.81% the percentage of patients with silent CAD missed at the screening. This study first shows that ED can improve the effectiveness in discriminating diabetic men to screen for asymptomatic CAD, when it is added to the list of RFs of the current screening guidelines.

Keywords Erectile dysfunction · Diabetes · Silent coronary disease · Screening · Guidelines

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Introduction

The prognosis of diabetes mellitus is severely driven by cardiovascular complications, in particular by coronary artery disease (CAD) [1, 2]. CAD occurs more frequently and is more severe in diabetic than in nondiabetic subjects [1, 2]. Death results from cardiovascular disease in about 75% of diabetic patients [1, 2]. In patients with diabetes early stage of CAD is often undetected and CAD is frequently diagnosed in advanced stage [1, 2]. In addition, in diabetic patients myocardial ischemia is often silent [3, 4]. Silent myocardial ischemia seems to be characterized by a poor prognosis, with a three- to fourfold increase in the risk for cardiovascular events [3, 4]. An early identification and treatment of asymptomatic CAD patients may significantly improve their cardiovascular prognosis [3, 4]. Some longitudinal studies have shown that erectile dysfunction (ED) can predict CAD in both diabetic and nondiabetic subjects [5–10]. Moreover, ED is strongly associated with subclinical atherosclerosis [11] and asymptomatic CAD angiographically documented in type 2 diabetic patients [12]. This has suggested that ED should be even considered as an "atypical" sign of CAD [13] or as a CAD risk equivalent [14]. Current guidelines suggest to perform screening for CAD in diabetic patients with some clinical conditions or in asymptomatic subjects with at least two additional risk factors (RFs) [15]. Nevertheless, recent studies have shown that a large proportion of diabetic patients with asymptomatic CAD can be missed on the basis of current guidelines [16, 17]. Since ED is considered a powerful marker of silent CAD [3–6, 11–13], in the present study we have evaluated whether it is possible to decrease the percentage of diabetic patients with silent CAD missed when ED is added to the list of RFs considered by the current screening guidelines.

Materials and methods

A total of 299 consecutive males with newly diagnosed type 2 diabetes mellitus were evaluated to find patients with asymptomatic CAD and to assess the presence of diabetic complications. Patients with type 1 diabetes mellitus, known vascular disease, with limited life-expectancy, or any clinical condition which requires testing for CAD according to the current screening guidelines [15] were excluded. In particular, specific exclusion criteria were: age <45 or >70 years, decreased C-peptide, positive anti-GAD antibodies, history of coronary events, symptoms of coronary events as defined by Rose questionnaire, atypical cardiac symptoms, history of artery revascularization, heart failure, abnormal resting ECG suggestive of myocardial ischemia or infarction, uncontrolled hypertension (>180/100 mmHg), atrial fibrillation or other important arrhythmias, significant valvular diseases, cardiomyopathy, chronic or acute diseases, neoplasia, previous stroke, claudicatio intermittens, ankle brachial index <0.9, and carotid occlusive artery disease as assessed by echocolordoppler.

The study protocol is depicted in Fig. 1. Among the 299 patients, 283 of them underwent an exercise stress testing, as previously described [8, 18–20]. Subjects were requested to discontinue any antihypertensive drug with antiischemic properties, including β-blockers and calcium channel blockers [8, 18–20]. An exercise ECG test was considered positive if there was a ST segment depression equal to or greater than 1 mm which was planar or

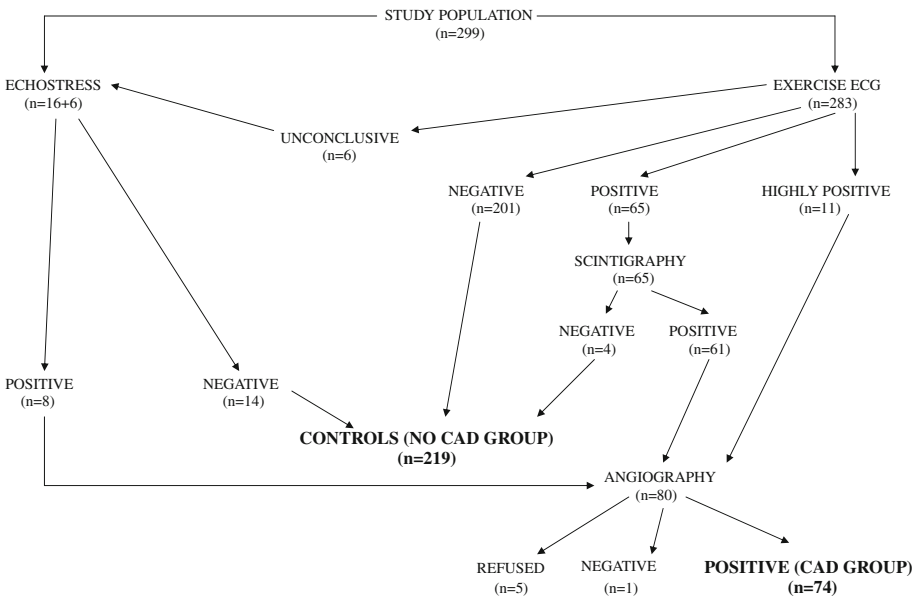

Fig. 1 The study protocol

downsloping and persisted for at least 80 ms after the J point ($n = 65$). A test was considered negative when the patient reached 90% of the maximal predicted exercise heart rate for age without symptoms and significant ST segment change ($n = 201$). When an exercise ECG test was highly positive (ST depression in 5 or more leads; >2 mm maximum ST depression; a positive test with a heart rate <120; hypotension during exercise; exercise capacity <5 min) the suspicion of CAD was considered strong ($n = 11$). In 6 patients ECG stress testing was inconclusive and therefore a dipiridamole stress testing was performed. In the other 65 patients with a positive exercise ECG test an exercise stress thallium scintigraphy was performed, as previously described [8, 18–20]. In particular, initial imaging was made within 5 min after intravenous injection of thallium-201. Four hours later, cardiac imaging was repeated. Five regions of the left ventricle were defined: anterior, apical, septal, inferior, and postero-lateral. The scintigraphy was considered positive for CAD when the thallium scan exhibited fixed or transient uptake defects. In patients with any condition which did not permit maximal exercise testing (e.g., traumatic amputation, foot wound, and severe obesity) or its interpretation (bundle branch block), and in those with an unconclusive stressing test a dypiridamole echostress was performed ($n = 22$), as previously described [8, 20]. Real time two dimensional echocardiografic examinations were performed before and after dypiridamole administration. The simultaneous comparison of the echocardiograms at rest and post-dypiridamole using a quad screen format was performed to identify regional wall motion abnormalities. The echo-stress was considered negative if no regional wall motion abnormalities were observed. In patients with highly positive ECG ($n = 11$), in those with a positive scintigraphy ($n = 61$) and in those with a positive dipiridamole stress testing ($n = 8$) a diagnostic coronary angiography was recommended and performed as previously reported [21]. An atherosclerotic lesion was considered significant when a stenosis ≥50% of the lumen in at least one major vessel was documented. Coronary angiography was performed in 75 subjects, since 5 patients refused. Among them, in 74 patients a significant asymptomatic CAD (CAD group) was documented. The NO CAD group ($n = 219$) included all the patients with negative non invasive testing: 201 with negative ECG stress testing, 61 with negative stress scintigraphy, and 14 with negative dypiridamole echostress.

Criteria to establish the diagnosis or the presence of diabetes, micro and macroalbuminuria, smoking habits, family history of CAD, and autonomic neuropathy were reported elsewhere [8, 12, 20]. Hypertension and dyslipidemia were defined according to the screening guidelines criteria [15] or in presence of a specific treatment.

Venous blood samples were taken from subjects after fasting for 12 h. Cholesterol, HDL, and triglycerides were measured by an automatic analyzer HITACHI 737 (Tokio-Japan). LDL was calculated by the Friedewald's formula [22]. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (Biorad, Richmond-CA). Albumin Excretion Rate (AER) was measured by nephelometry (Beckmann, Milan-Italy).

ED assessment

The presence and the degree of ED were assessed by the validated International Index Erectile Function-5 (IIEF-5) questionnaire [23]. ED was considered present, when IIEF-5 score was ≤21 [23]. All patients gave their informed consent both to perform each test and to participate in the study and the study protocol was approved by the institution's human research committee.

Statistical analysis

Differences in normal variables were assessed by the Student *t*-test and differences in non normal variables by the Mann–Whitney *U*-test. The Pearson Chi-squared test was used for frequency comparison. The effect of several variables on the presence of asymptomatic CAD was tested by the stepwise Cox regression analysis. The following variables were tested: HbA1c, BMI, cholesterol, triglycerides, LDL, HDL, hypertension, dyslipidemia, family history of CAD, smoking, microalbuminuria/macroalbuminuria, pharmacologic treatment, autonomic dysfunction, and ED. Variable were dichotomized as previously reported [8, 12, 20]. Hypertension and dyslipidemia were defined according to the screening guidelines criteria [15] or in presence of a specific treatment. Odd ratios (ORs) with their 95% Confidence Interval (95%CI) were computed to identify significant predictors of asymptomatic CAD. A multiple stepwise regression analysis was used to predict CAD among male patients. HbA1c, BMI, cholesterol, triglycerides, LDL, HDL, hypertension, dyslipidemia, family history of CAD, smoking, Albumin Excretion Rate (AER), pharmacologic treatment, autonomic dysfunction, and IIEF-5 score were tested as potential predictors. A forward selection procedure was used. The criterion for inclusion into the model as an independent variable is a P-value < 0.05, as determined with the F-test. Sensitivity (probability that a test will be positive when the disease is present), specificity (probability that a test will be negative when the disease is not present), positive predictive value (probability that the disease is present when the test is positive), and negative predictive value (probability that the disease is not present when the test is negative) have been calculated for the screening of

asymptomatic CAD. A P-value < 0.05 was considered statistically significant.

Results

Table 1 shows biological and clinical characteristics of the whole study population and of the male patients subdivided into two groups according to the presence/absence of CAD. As shown, total cholesterol and the prevalence of smokers, family history of CAD, micro/macroalbuminuria, and ED were significantly higher in CAD than in NO CAD patients. No significant differences in the prevalence of hypertension or dyslipidemia, as defined according to the current screening guidelines [15], were observed between the groups.

Table 2 reports the percentages of patients with at least two RFs of the current guidelines, of those with only one RF and of those with two RFs, if ED is added to the list of the criteria of the current guidelines. As shown, if current criteria are used, the screening for CAD should be performed only in 62.2% of patients with asymptomatic proven CAD. When ED is added to the list of the RFs, the percentage of CAD patients in whom screening should be recommended increases to 89.2% in the CAD group, but the percentage of patients to screen in the no CAD group only slightly would increase, from 39.2 to 42.0%. Therefore, if ED is added to the list of the risk factors of the current guidelines, the percentage of patients with asymptomatic CAD missed to the screening decreases from 37.8 to 10.2%.

Sensitivity, specificity, and positive or negative predictive values have been calculated for the screening for CAD when current screening guidelines were used (Sensitivity: 0.62; specificity: 0.60; positive predictive value: 0.34; negative predictive value: 0.82), and for the screening for CAD when ED was added to the current criteria (Sensitivity: 0.89; specificity: 0.57; positive predictive value: 0.41; negative predictive value: 0.94).

CAD severity and screening for asymptomatic CAD

Among the CAD patients submitted to coronary angiography, 21 (28.4%) showed a single-vessel disease, 24 (32.4%) a two-vessel disease, and 29 (39.2%) a three-vessel disease. Among the 46 of the 74 CAD patients who satisfy current screening criteria, 8 (17.4%) had a single-vessel disease, 15 (32.6) a two-vessel disease, and 23 (50.0%) a three-vessel disease. Among the 20 patients with only one RF and ED, 9 (45%) showed a single-vessel disease, 6 (30%) a two-vessel disease, and 5 (25%) a three-vessel disease. Therefore, CAD severity was significantly greater in CAD patients who satisfied current criteria versus those with only one RF and ED: χ^2: 6.208 (DF = 2); $P = 0.0450$.

Table 1 Features of the whole study population and of male patients stratified by presence/absence of coronary artery disease (CAD)

	All patients	CAD group	NO CAD group	*P*
Number	293	74	219	
Age (years)	56.6 ± 5.9	55.6 ± 4.8	57.1 ± 6.2	0.079
BMI	27.0 ± 3.6	26.5 ± 3.6	27.2 ± 3.5	0.223
HbA1c (%)	7.8 ± 1.2	8.0 ± 1.3	7.8 ± 1.1	0.093
Cholesterol (mg/dl)	205.0 ± 28.6	211.9 ± 30.2	202 ± 27.7	0.017
LDL (mgl/dl)	126.0 ± 29.4	131.2 ± 29.4	124.3 ± 29.2	0.082
HDL (mg/dl)	44.9 ± 8.7	44.5 ± 8.0	45.0 ± 9.0	0.687
Triglycerides (mg/dl)	170.7 ± 62.9	181.2 ± 70.3	167.1 ± 59.9	0.095
Dyslipidemia[a] (%)	50.2	43.2	52.5	0.168
Micro/macroalbuminuria (%)	15.0	27.0	11.0	0.008
AER (mg/day)	38.6 ± 99.4	64.8 ± 148.9	29.7 ± 74.2	<0.001
Smokers (%)	24.6	55.4	14.2	<0.001
Family history of CAD (%)	20.1	32.4	16.0	0.002
Hypertension[a] (%)	54.6	45.9	57.3	0.084
Autonomic neuropathy (%)	6.5	8.1	5.9	0.511
ED (%)	20.8	37.8	15.1	<0.001
IIEF-5 score	21.6 ± 6.0	18.4 ± 8.0	22.6 ± 4.6	<0.001

AER albumin excretion rate, *IIEF-5* international index erectile function—5

[a] Defined according to the current criteria of screening guidelines or in presence of specific treatment

Table 2 Percentage of patients stratified by the number of risk factors (RFs) of the current guidelines for the screening of coronary artery disease (CAD) and the presence of erectile dysfunction (ED) in the CAD and NO CAD group

	CAD (n = 74)	NO CAD (n = 213)	*P*-value
Only one RF	35.1	55.2	0.0027
Only one RF + ED	27.0	2.7	<0.0001
At least 2 RFs	62.2	39.3	0.0007
At least 2 RFs, including ED	89.2	42.0	<0.0001

Multivariate analyses

In order to evaluate the impact of each RF in predicting asymptomatic CAD in male diabetic patients, a multivariate Cox regression analysis was performed. The independent predictors of CAD were smoking (OR: 7.8; 95%CI: 4.0–15.2; $P < 0.0001$), ED (OR: 4.4; 95%CI: 2.1–9.0; $P < 0.0001$), micro/macroalbuminuria (OR: 2.8; 95%CI: 1.3–6.3; $P = 0.009$), and family history for CAD (OR: 2.3; 95%CI: 1.1–4.8; $P = 0.017$). Presence of dyslipidemia and hypertension did not enter the regression model. Stepwise multiple regression analysis showed that smoking, IIEF-5 score, AER, and family history of CAD were significantly associated with silent CAD in diabetic men (Table 3).

Pharmacologic treatment

No difference in the percentage of patients treated with antihypertensive drugs was observed between CAD and NO CAD patients: 37.8 versus 43.8%; χ^2: 1.65 (DF = 1); $P = 0.1986$. The percentage of patients treated with statins was significantly lower in the CAD than in the NO CAD group: 35.1 versus 48.9%; χ^2: 4.20 (DF = 1); $P = 0.0404$. However, in multivariate analyses antihypertensive drugs and statins were not independently associated with silent CAD.

Table 3 Results of a multiple regression analysis (forward selection procedure) with presence/absence of asymptomatic CAD (coronary artery disease) as the dependent variable

Predictor	Step	F to enter	β	Multiple R^2	*P*-value
Smoking	1	61.0	0.37	0.17	<0.001
IIEF-5 score	2	22.4	−0.22	0.23	<0.001
AER	3	7.0	0.13	0.25	0.008
Family history of CAD	4	4.5	0.13	0.26	0.033

IIEF-5 international index erectile function-5, *AER* albumin excretion rate

Discussion

ED is considered a strong predictor of CAD both in diabetic and in nondiabetic subjects [3, 5, 6], since several longitudinal studies have documented that ED is able to predict the future development of cardiovascular events [7–10]. In addition, ED seems to be a powerful marker of silent or subclinical atherosclerosis [11, 12] and therefore has been suggested as an atypical sign of CAD [13] or as a CAD risk equivalent [14]. Indeed, ED is an early marker of an endothelial dysfunction due to several traditional RFs [3, 5, 6], although several other conditions, including hormonal factors, including hypogonadism, can affect endothelial function [24] and cause ED [5, 6].

The present study first shows the role of ED in increasing the percentage of diabetic males with asymptomatic CAD who may benefit from the screening for CAD. Recent large studies showed that about 40% of patients with asymptomatic CAD can be missed on the basis of current guidelines for the screening of CAD [16, 17]. This means that in many patients the diagnosis of occult CAD is delayed and this can worsen their cardiovascular prognosis [3, 4]. A recent large randomized study has suggested that cardiac outcomes are not significantly reduced by systematic screening for CAD in diabetes [25], but other studies have shown that the early identification of diabetic patients with asymptomatic CAD can reduce cardiovascular morbidity and mortality [20, 26–31]. This maybe due to an early revascularization, specific interventions, and more frequent clinical evaluations [3, 4, 20, 26–31]. In particular, the BARI2D study has recently suggested that coronary revascularization in addition to optimal medical therapy can improve cardiovascular prognosis [31]. However the impact of the screening for CAD on the cardiovascular prognosis should be definitively clarified by specific intervention studies [4, 20].

We enrolled newly diagnosed diabetic patients not only to avoid some pharmacological and clinical interferences but also for clinical purposes. In newly diagnosed patients the interference of diabetes drugs is not present and the interference of other treatments regarding RFs can be limited. This is particularly true for dyslipidemia. In fact, diabetic patients should have LDL levels <100 mg/dl [32]. This implies that virtually all diabetic patients should take statins; thus they are considered to have dyslipidemia according to current screening guidelines [15]. Moreover, the enrollment of newly diagnosed patients eliminates some important confounding factors, such as diabetes duration and glycemic control. Lastly, in the clinical practice the screening for CAD should be early enough to really detect less severe CAD, thereby at diagnosis of diabetes being the ideal timing. Our study clearly shows that if current criteria of guidelines [15] are used, the

screening for CAD should be performed in 62.2% of our patients with asymptomatic CAD. This implies that about 37.8% of the patients with occult CAD are missed, confirming previous studies [16, 17]. Current guidelines are characterized both by low specificity and sensitivity (62 and 60% in our hands, respectively). When ED is added to the list of criteria included in the current guidelines, screening became advisable in 89.1% of our patients with silent CAD. So, if ED is added to the list of RFs, the percentage of the patients with CAD missing the screening would decrease from 37.8 to 10.8%, with a concomitant only slight increase in the number of patients to be screened in the NO CAD group (from 39.2 to 42%). In other words, ED seems to highly increase the sensitivity of the current guidelines without a significant variation in specificity. In addition, both positive and negative predictive value of the screening can increase significantly, when ED is used. In particular, the negative predictive value is particularly high: this may imply that many tests can be avoided in patients without CAD.

Table 2 shows that there is a significantly higher percentage of patients with only one RF in the NO CAD than in the CAD group. Nevertheless, ED shows a high association with silent CAD and it is able to select patients with only one RF among the CAD patients. Indeed, when ED is added to the list of predictors, it can discriminate among the patients with only one RF those to screen for CAD. On the other hand, the multivariate analyses show that both ED and IIEF-5 score are strong independent predictors of occult CAD and that their predictive power is even greater than that of other criteria of the current guidelines, such as microalbuminuria and family history for CAD. This suggests that ED can have an important role not only in the individual cardiovascular risk stratification [33, 34] but also in the decision to screen diabetic patients for CAD.

Current guidelines seem to be mainly effective in the identification of patients with a greater CAD severity, as shown by the angiographic analysis. Indeed the majority of the patients identified by the current guidelines have a three-vessel disease. On the contrary, the majority of CAD patients with only one RF and ED have a lower CAD severity. This suggests that ED may improve the effectiveness of the current screening guidelines in the identification of subjects with CAD at an earlier stage. This strategy for earlier detection of CAD may lead to more effective reduction of cardiovascular morbidity and mortality.

In conclusion, our data suggest that to improve the effectiveness of the screening guidelines additional predictors should be added to current criteria. Several previous studies observed an association between silent CAD and some predictors, such as age >60 years [35], autonomic neuropathy [16, 36, 37], retinopathy [28], genetic risk factors [18, 19], insulin-resistance [38], but the impact of these RFs on the screening for CAD in diabetes remains unclear [39]. The present study first has shown that ED is able to increase the effectiveness of current guidelines, at least in newly diagnosed men with type 2 diabetes. Therefore sexual function should be routinely evaluated in all diabetic men at the moment of the diagnosis of diabetes by using the simple validated self-administered 5-item questionnaires, called IIEF-5 [5, 6] and the screening for CAD should be performed in all ED diabetic men with at least another RF.

Conflicts of interest None.

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