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Letter to the Editor · **Open Access** ·

Erectile dysfunction as a predictor of asymptomatic coronary artery disease in elderly men with type 2 diabetes

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1 Introduction

Erectile dysfunction (ED) and coronary artery disease (CAD) are closely linked, as both conditions share the same cardiovascular risk factors.[1] Indeed, these risk factors can determine endothelial dysfunction that represents the common underlying mechanism of both ED and CAD.[1,2]

The prevalence of ED is about three-fold higher among diabetic patients than in the general population[1,3] and a higher prevalence of CAD has been observed in people with diabetes when compared to non-diabetic subjects.[3] Some studies showed that ED can be a powerful marker of silent CAD[4,5] and a strong predictor of cardiovascular events in apparently uncomplicated type 2 diabetic patients.[6,7] Therefore ED is now considered as a sentinel symptom of silent CAD, as ED often precedes the onset of myocardial ischemia itself by many years.[2,8,9]

Silent CAD can worse the prognosis of diabetic patients and this suggests to identify diabetic patients at higher risk for silent CAD in order to early and effectively treat them.[10–13] Current guidelines suggest the screening for CAD when diabetic patients have some clinical conditions or at least two cardiovascular risk factors in addition to diabetes.[14] Unfortunately several studies showed that about 40% of diabetic patients with silent CAD can be missed on the basis of the current guidelines,[15,16] but ED may interestingly improve sensitivity and specificity of guidelines for CAD screening when it is added to the common cardiovascular risk factors.[16]

ED is the most frequently diagnosed sexual dysfunction in the older male population, especially after 70 years, even if it is often underreported and under-diagnosed in the elderly.[17] In addition, CAD prevalence increases with age. So it may be of great interest to understand whether ED remains a risk factor for silent CAD in elderly diabetic patients. To the best of our knowledge, no study has specifically investigated the role of ED as a predictor of silent CAD in type 2 diabetic elderly subjects. Therefore, the aim of the present study was to evaluate whether ED may be a marker of asymptomatic CAD also in elderly patients with diabetes.

2 Methods

A population of 328 consecutive males with type 2 diabetes mellitus were enrolled in this study. All the patients attending at the outpatient diabetic clinic for the first time were recruited. Exclusion criteria were: type 1 diabetes mellitus, decreased C-peptide, positive anti-GAD antibodies, limited life-expectancy, any chronic or acute disease, malignancies, any known or suspect cardiovascular disease, such as history of coronary events or artery revasculariza-

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tion, 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, previous stroke, claudicatio intermittens.

To assess the presence of asymptomatic CAD an exercise stress testing was performed in all the subjects; alternatively a dipyridamole stress testing was performed in people with any condition that did not permit maximal exercise testing (such as severe obesity, foot wound, and so on) or in those with inconclusive exercise stress testing. Procedures for exercise stress testing and dipyridamole stress testing and criteria for the diagnosis of asymptomatic CAD were reported elsewhere.[4,16] In patients with a positive noninvasive testing for CAD a coronary angiography was proposed. Angiography was performed as previously described.[18] A coronary lesion was considered significant when a stenosis ≥ 50% of the lumen was observed.

All criteria for the diagnosis of type 2 diabetes, hypertension, dyslipidemia, presence of micro and macroalbuminuria, smoking habits, family history of CAD were previously reported.[4,6,11]

Venous blood samples were taken from the patients after fasting for at least 12 h. Cholesterol, high-density lipoprotein (HDL) and triglycerides were measured by an automatic analyzer HITACHI 737 (Tokio, Japan). Low-density lipoprotein (LDL) was estimated by the Friedewald's formula.[19] Albumin excretion rate (AER) was assessed by nephelometry (Beckmann, Milan, Italy). Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (Biorad, Richmond, USA).

The presence of ED was assessed by the validated International Index Erectile Function-5 (IIEF-5) questionnaire.[20] ED was defined as an IIEF-5 score < 21.[20]

The study was approved by the local ethics committee. All patients gave their informed consent both to participate in the investigation and to perform each test.

Univariate analysis was performed with Student *t*-test to assess differences in normally distributed variables, while Mann-Whitney *U*-test was used in non-normally distributed parameters. The Pearson Chi-squared test was used for frequency comparison. The following variables were tested as potential predictors of silent CAD in a multiple logistic regression analysis: body mass index, HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, micro/macroalbuminuria, smoking, family history of CAD, hypertension and ED. Variables were dichotomized as previously reported.[4,6,11] A P value < 0.05 was considered statistically significant.

3 Results

The study population of 328 men was divided by age into two groups: 213 subjects were aged ≤ 65 years (Group A) and 115 men were older than 65 years (Group B). Each group was stratified by the presence/absence of asymptomatic CAD angiographically proven.

Table 1 shows clinical and biochemical features of the Group A stratified by presence/absence of CAD. As shown, younger diabetic patients with silent CAD have a significant greater prevalence of micro/macroalbuminuria, smokers, family history for CAD and ED than those without silent CAD.

Table 2 shows clinical and biochemical features of the Group B stratified by presence/absence of CAD. As shown, older diabetic patients with silent CAD have a significant greater prevalence of micro/macroalbuminuria, smokers and family history for CAD than those without silent CAD. There is no significant difference in the prevalence of ED between patients with and those without silent CAD among older patients.

Both among younger and older patients a multivariate Cox logistic regression analysis was performed with presence/absence of silent CAD as the dependent variable. In the GROUP A the analysis showed that smoking habits

Table 1. Features of the male patients aged between 45 and 65 years stratified by presence/absence of CAD.

	All patients	CAD group	No CAD group	*P*
n	213	45	168	
Age, yrs	56.6 ± 5.7	55.7 ± 5.0	57.0 ± 6.1	0.101
BMI, kg/m^2	28.4 ± 3.8	27.6 ± 3.7	28.7 ± 3.5	0.119
HbA1c,%	8.1 ± 1.2	8.0 ± 1.3	8.2 ± 1.1	0.277
Cholesterol, mg/dL	207.0 ± 29.5	213.1 ± 29.1	203.1 ± 28.6	0.011
LDL, mg/dL	128.4 ± 30.0	132.1 ± 30.1	124.4 ± 29.9	0.065
HDL, mg/dL	44.8 ± 8.8	44.2 ± 7.9	45.2 ± 8.9	0.578
Triglycerides, mg/dL	165.1 ± 66.6	186.3 ± 73.9	162.8 ± 61.8	0.059
Micro/Macroalbuminuria, %	21.1	46.6	14.2	< 0.001
Smokers, %	26.2	68.8	14.8	< 0.001
Family history of CAD, %	24.4	33.3	5.4	< 0.001
Hypertension*, %	58.2	55.5	58.9	0.683
ED, %	19.7	31.1	16.6	0.030

Data are presented as mean ± SD unless other indicated. *Defined according to the current criteria of screening guidelines or in presence of specific treatment. BMI: body mass index; CAD: coronary artery disease; ED: erectile dysfunction; HbA1c: haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 2. Features of the male patients aged between 66 and 75 years stratified by presence/absence of CAD.

	All patients	CAD group	No CAD group	*P*
n	115	37	78	
Age, yrs	69.6 ± 2.8	70.0 ± 2.9	69.3 ± 2.6	0.253
BMI, kg/m^2	28.1 ± 3.8	28.0 ± 3.8	28.2 ± 3.9	0.751
HbA1c, %	8.6 ± 1.3	8.8 ± 1.3	8.5 ± 1.2	0.174
Cholesterol, mg/dL	203.0 ± 29.0	205.9 ± 29.1	201.2 ± 28.8	0.251
LDL, mg/dL	122.1 ± 28.9	124.2 ± 30.1	121.8 ± 27.9	0.189
HDL, mg/dL	44.2 ± 8.4	44.0 ± 8.0	45.3 ± 8.5	0.711
Triglycerides, mg/dL	159.7 ± 55.1	163.1 ± 64.9	153.3 ± 61.2	0.391
Micro/Macroalbuminuria, %	25.2	51.3	12.8	< 0.001
Smokers, %	21.7	51.3	7.8	< 0.001
Family history of CAD, %	20.0	43.3	6.4	<0.001
Hypertension*, %	71.3	67.5	73.1	0.231
ED, %	42.6	48.6	39.7	0.364

Data are presented as mean ± SD unless other indicated.*Defined according to the current criteria of screening guidelines or in presence of specific treatment. BMI: body mass index; CAD: coronary artery disease; ED: erectile dysfunction; HbA1c: haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

(OR: 8.51; 95% CI: 4.11–16.47; P < 0.001), micro/macroalbuminuria (OR: 6.11; 95% CI: 3.46–14.61; P < 0.001), family history of CAD (OR: 2.9; 95% CI: 1.29–6.45; P = 0.007) and ED (OR: 1.87; 95% CI: 1.02–7.31; P = 0.046) were significant predictors of silent CAD. In the Group B the analysis showed that microalbuminuria (OR: 5.78; 95% CI: 2.13–12.97; P < 0.001) and smoking habits (OR: 2.65; 95% CI: 2.13–6.21; P = 0.004) were significant predictors of silent CAD. ED does not enter the model.

4 Discussion

Previous studies showed that ED can be a powerful marker of asymptomatic CAD,[1–4,16] and that it may significantly increase sensitivity and specificity of the current guidelines on the screening of CAD in diabetes.[16] The present investigation shows that ED can be an useful tool to better identify subjects to screen for CAD among younger but not among older type 2 diabetic patients. Indeed, our data confirm the strong independent association between ED and silent CAD only in subjects aged 65 years or younger, but no association was observed in older patients both in univariate and multivariate analysis. This novel finding may be due to several reasons. As it is well-known, the prevalence of ED increases with age and this is caused by many factors in addition to vascular impairment.[21] Hormonal changes are usually observed in elderly people and they can play a major role in the occurrence of ED.[22] The Massachusetts Male Aging Study demonstrated that testosterone declines at a rate of 1%–2% a year.[23] Free testosterone levels are reduced up to 30% in the 7th decade. Sex hormone binding globulin binds a higher percentage of total testosterone, up to 75%, reducing the amount of bio-available androgen. Luteinizing hormone is higher in the elderly, suggesting secondary hypogonadism.[23] Other conditions are able to increase the occurrence of ED independently of vascular damage Among them, an important role is played by lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) that are very common in elderly subjects.[24] In addition many co-morbidities, including hypertension, and their treatments are more frequent in older than in younger patients and they can favor the development of ED also in subjects without significant vascular disease.[1,21] All these conditions can greatly affect the predictive power of ED for silent CAD in elderly people and this may explain our data.

Silent CAD is a frequent complication in diabetes, but conflicting data are available in the literature on the potential effects of a systematic screening for unknown on the prognosis. Two large randomized controlled studies have shown that a systematic screening for CAD does not improve the cardiovascular prognosis in diabetic subjects,[25,26] even if other work found opposite conclusions.[11,27] However, at the moment a systematic screening for CAD is not recommended,[13] but additional data are considered to be necessary.[10–13]

It is interesting to note that current guidelines for CAD screening may have their best predictive power in diabetic patients aged 60 years or more.[28] Our data suggest that ED may further increase the predictive power of current guidelines to identify who to screen for occult CAD among younger people with diabetes, even if ED seems to have no importance in older patients. However, the systematic assessment of ED remains important in all people with diabetes, since it permits not only to better stratify the individual cardiovascular risk but also to improve the quality of life.[29] To better estimate the risk for silent CAD in elderly diabetic patients, other risk factors may be evaluated, such as genetic risk factors,[30–32] diabetic retinopathy,[33] disautonomic neuropathy.[15] At last, it is important to remember that peripheral artery disease is considered a strong predictor for CAD,[14] but this condition is often underdiagnosed.[34]

Even if our study for the first time has shown the decreased predictive power of ED in the identification of silent CAD in elderly subjects with diabetes, it has some limitations. First, we do not have data on hormone profile, LUTS and BPH that may help to understand the reasons for our results. Second, the study population may be relatively small. Therefore larger studies should confirm our findings.

In conclusion, the present study first suggests that ED seems to be not associated with silent CAD in type 2 diabetic patients aged 66 years or older and thus it may lose the important role of marker of occult CAD in the elderly diabetic population. However our data confirm that ED is a reliable predictor of silent CAD in younger diabetic patients.

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