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Subclinical Coronary Artery Atherosclerosis in Patients With Erectile Dysfunction

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OBJECTIVES The purpose of our study was to assess the prevalence and extent of coronary artery atherosclerosis in asymptomatic patients with vascular erectile dysfunction (ED).

BACKGROUND An association between ED and ischemic heart disease has been suggested, but it is unknown if it represents a marker of subclinical coronary atherosclerosis.

METHODS We studied 70 consecutive patients with vascular ED, evaluated by penile Doppler, and 73 control subjects with no history of coronary artery disease. We measured traditional coronary risk factors, circulating levels of C-reactive protein (CRP), endothelial function by ultrasound of brachial artery, and coronary artery calcification by multi-slice computed tomography.

RESULTS The patients and the control group were similar for age, race, and coronary risk score. Patients with ED had significantly higher high-sensitivity C-reactive protein levels (2.62 vs. 1.03 mg/l, $p < 0.001$). Flow-mediated dilation of the brachial artery was more impaired in patients with ED than in controls (2.36 vs. 3.92, $p < 0.001$). Coronary artery calcification was more frequent in individuals with ED than in control subjects ($p = 0.01$). Multiple logistic regression analysis showed that patients with ED had an overall odds ratio of 3.68 for having calcium score above the 75th percentile, compared to the controls.

CONCLUSIONS Coronary atherosclerosis is more severe in patients with vascular ED; ED predicts the presence and extent of subclinical atherosclerosis independent of traditional risk factors for cardiovascular disease. Thus, ED may be considered an additional, early warning sign of coronary atherosclerosis. (J Am Coll Cardiol 2005;46:1503–6) © 2005 by the American College of Cardiology Foundation

Erectile dysfunction (ED), defined as the recurrent or persistent inability to attain and/or maintain an erection in order for satisfactory sexual performance, is present in up to 30 million men in the U.S. and approximately 100 million men worldwide (1).

Several studies have shown that most cases of ED recognize a vascular etiology and are associated with hypertension and diabetes (2,3). Other studies have reported a high prevalence of ED in patients with coronary artery disease (CAD) and a significant correlation between the severity of ED and the number of vessels involved (4), but little is known about the prevalence, extent, and causes of coronary artery atherosclerosis in ED patients without symptomatic CAD. Coronary artery atherosclerosis can be detected noninvasively with the use of multi-slice computed tomography (MSCT) (5). The extent of coronary artery calcification (CAC) correlates with findings on coronary angiography and with the extent of atherosclerosis in pathological specimens and is predictive of future cardiac events (6,7). We hypothesize that the prevalence and extent of CAC are higher in patients with ED, as compared with a control group matched for age, race, and coronary risk score.

METHODS

Subjects and study design. Between January 2003 and November 2004, we studied 70 patients with ED and 73 control subjects who were frequency-matched for age, race, (all Caucasian), and coronary risk score. Patients were recruited from the local endocrinologic clinic specializing in male sexual dysfunction. Control subjects were recruited by advertisement and from a database of volunteers maintained by the Policlinico Hospital at Modena University School of Medicine. Erectile dysfunction was evaluated by using the International Index of Erectile Function (IIEF-5) (8), an abbreviated form of the IIEF used to classify ED, with four items selected from the erectile domain portion of the IIEF and one addressing sexual satisfaction. The degree of ED is classified by the erectile function domain score as complete (≤4), severe (5 to 10), moderate (11 to 14), mild (15 to 18), or none (19 to 20).

Patients with ED underwent a penile Doppler examination to exclude nonvascular causes of ED. Information was obtained through an interview, physical examination, laboratory tests, vascular reactivity, MSCT, and, in the case of patients, penile Doppler examination.

We calculated an expected 10-year risk of cardiac death or nonfatal myocardial infarction with range estimates

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Abbreviations and Acronyms

CAC = coronary artery calcification
CAD = coronary artery disease
ED = erectile dysfunction
FMD = flow-mediated dilation
IIEF = International Index of Erectile Function
MSCT = multi-slice computed tomography
NMD = nitroglycerin-mediated dilation

published within the National Cholesterol Education Panel III risk calculator (9).

Penile Doppler examination. Penile Doppler studies were performed using the Knoll/Midus ultrasonic velocitometric system (Urometrics, St. Paul, Minnesota). Measurement included peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index ($RI = PSV - EDV/PSV$). All patients received 10 to 20 μg of intracavernosal prostaglandin E-1, and measurements were performed at 5 and 15 min after injection to determine the PSV, EDV, and RI. Erectile dysfunction was determined to be vascular in origin if PSV was <35 cm/s or RI was <0.9 (10).

Brachial artery reactivity. An ultrasound study of the brachial artery was performed in all participants by means of an Acuson 128 XP/10 mainframe with a 7.0-MHz linear array transducer (Acuson, Mountain View, California). The technique for assessing brachial artery flow-mediated dilation (FMD) has been described in detail elsewhere (11). In brief, FMD was assessed by measuring the change in brachial artery diameter after 60 s of reactive hyperemia compared with baseline measurements after deflation of a cuff placed around the forearm that had been inflated to 50 mm Hg above systolic blood pressure for 5 min. Increase in diameter after sublingual nitroglycerin (0.4 mg) was used as a measure of endothelium-independent vasodilation nitroglycerin-mediated dilation (NMD). The response of the vessel diameter to reactive hyperemia and nitroglycerin was expressed as percent change relative to the diameter immediately before cuff inflation and to the diameter immediately before drug administration, respectively.

Coronary calcification. All subjects were examined with a Light Speed Plus multi-slice scanner (GE Medical Systems, Milwaukee, Wisconsin). All images were obtained in a single breath hold using 320 mAs and 140 Kv. A section thickness of 2.5 mm, a field of view of 20 cm, and a matrix of 512 × 512 were used to reconstruct the raw image data, yielding a nominal pixel size of 0.39 × 0.39 mm^2 and a voxel volume of 0.4 mm^3. Image acquisition was triggered to the 80% R-R interval. Images were then transferred to a workstation that enables coronary calcium quantification by means of the "Smart Score" software (GE Medical Systems). The degree of CAC was calculated according to both Agatston and volume score, as previously described (12,13). We chose to report only calcium score based on volumetric method, because this measure is known to be better reproducible and comparable and represents a physical quantitative measure.

Statistical analysis. Data are expressed as mean ± SD, median (and interquartile range) for variables with a skewed distribution, or percentage. Comparisons between patients with ED and controls were made by means of two-sample *t* tests or Mann-Whitney *U* tests (in the case of non-normal distribution) for continuous variables and by chi-square analysis for categorical variables. The prevalence of CAC (percent with positive scores >0), as well as the prevalence of coronary calcification at/or above the median and 75th percentile, were compared between ED patients and control subjects. The independent association between ED and CAC was estimated by using multiple logistic regression analysis performed after adjustment for traditional coronary risk factors. Odds ratios and their 95% confidence intervals were reported. The difference in the rates of increase in the prevalence of CAC according to age between patients and controls was also assessed by using logistic regression. Statistical significance was deemed to be $p < 0.05$.

RESULTS

The two groups were similar in respect to all demographic variables and risk factors for coronary disease (Table 1). The mean IIEF-5 score was 12.7 ± 1.5 in the ED group and 22.1 ± 1.4 in the control group ($p < 0.001$). All ED patients had evidence of penile vascular disease. Mean peak systolic velocity measured by penile Doppler was 27.5 ± 3.5 m/s. Patients with ED had significantly higher high-sensitivity C-reactive protein levels (hs-CRP) (median 2.62; interquartile range: 2.05 to 3.44 mg/l vs. median 1.03; interquartile range: 0.78 to 1.26 mg/l; $p < 0.001$).

Brachial artery FMD was significantly lower in ED patients compared to the controls (2.36 ± 1.75 vs. 3.92 ± 2.2; $p < 0.001$); conversely, NMD was not statistically different between the two groups (8.36 ± 3.27 vs. 9.50 ± 3.50; $p = 0.09$).

The prevalence of CAC and calcium score in ED patients and control subjects is shown in Table 2.

The overall prevalence was higher among the patients than the controls (odds ratio 2.57; 95% confidence interval, 1.26 to 5.26; $p = 0.01$). Mean CAC score was 32.4 ± 59.2 (range 0 to 380) in the controls and 143.3 ± 230 (range 0 to 1,470) in the patients. Low and high levels of CAC were defined with the use of a calcium score above or below the median calcium score of patients with calcification (65, according to the volumetric method). In the patients, the odds ratios for having high levels of coronary calcification (with the absence of calcification used as the reference level) were 6.35 (95% confidence interval, 2.35 to 17.16). Among ED patients, 41.4% had a calcium score above the 75th percentile compared with 19.1% of the control group ($p < 0.004$) (Table 2). The results did not change significantly by using multiple logistic regression analysis adjusted for the Framingham risk score, diabetes, and body mass index.

Table 1. Clinical Characteristics of Patients With Erectile Dysfunction and Controls

Characteristics	Patients (n = 70)	Controls (n = 73)	p Value
Age, yrs	50.9 ± 6.7	50.1 ± 6.2	0.48
Diabetes, %	14.3	9.6	0.39
Smokers, %			
Never	65.7	65.8	0.73
Current	24.3	20.6	
Former	10.0	13.7	
Family history, %	22.9	21.9	0.89
Systolic pressure, mm Hg	132.5 ± 10.7	133.3 ± 10.7	0.64
Diastolic pressure, mm Hg	78.4 ± 5.9	79.2 ± 6.1	0.71
Body mass index, kg/m^2	27.9 ± 2.8	27.1 ± 2.5	0.08
Total cholesterol, mg/dl	193.9 ± 51.7	194.3 ± 46.9	0.96
Low-density lipoprotein, mg/dl	113.2 ± 39.0	112.1 ± 31.6	0.86
High-density lipoprotein, mg/dl	50.5 ± 13.4	50.9 ± 13.9	0.88
Triglycerides, mg/dl	121.2 ± 58.8	119.8 ± 54.6	0.89
Glycemia, mg/dl	106.2 ± 17.4	103.4 ± 15.2	0.32
Lipoprotein (a), mg/dl	23.9 ± 13.3	22.8 ± 7.9	0.83‡
C-reactive protein, mg/dl*	2.62 (2.05–3.44)	1.03 (0.78–1.26)	<0.001
Framingham risk score	7.2 ± 5.0	7.1 ± 4.8	0.96
Erectile dysfunction score†	12.7 ± 1.5	22.1 ± 1.4	<0.001
Penile Doppler PSV, cm/s	27.5 ± 3.5	—	—

Values are percentages or mean ± SD. *Values are presented as median with interquartile range; †based on the five-item International Index of Erectile Function; ‡Mann-Whitney *U* test was used.
PSV = peak systolic velocity.

Coronary artery calcification occurred at a younger age in ED patients than in control subjects, and the rate of increase in the prevalence of calcium with age was significantly higher in patients than in control subjects (p = 0.01) (Fig. 1).

DISCUSSION

The main finding in our study is that the prevalence and extent of asymptomatic atherosclerosis, as detected by MSCT, is significantly higher among patients with ED and cannot be predicted by the presence of traditional risk factors for cardiovascular disease. We also found that patients with ED had significantly impaired endothelial-dependent FMD and subclinical inflammation compared to the controls. These data suggest that ED may be the earliest manifestation of a generalized vascular disease and that these patients may be at an increased risk of later developing CAD.

On the basis of current knowledge of erectile physiology, the close relation between ED and coronary disease does not represent a surprise (14). Indeed, ED is often an expression of endothelial dysfunction, an early event in the atherosclerotic process. Kaiser et al. (15) reported a study of 30 patients with ED and no significant cardiovascular risk factors, well matched with a control group of normal subjects, and found an abnormal endothelial-dependent flow-mediated vasodilation in the brachial artery only in patients with ED. The difference between the last cited study and the present one is that our population presented a higher profile of CAD risk. However, the impaired endothelial function, noted in patients with ED in our study, could not be attributed to the presence of traditional cardiovascular risk factors because there were no differences compared to the control group with respect to Framingham risk score. In patients with ED, we also found significantly higher hs-CRP levels, an expression of subclinical chronic inflammation, compared with control subjects. Recent evidence suggests that CRP directly affects the vascular endothelium by inducing chemokines and adhesion molecules

Table 2. Prevalence of Coronary Artery Calcification and Calcium Score in Cases and Controls

Variables	Cases (n = 70)	Controls (n = 73)	Unadjusted		Adjusted	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Coronary artery calcification	75.7	54.8	2.57 (1.26–5.26)	0.01	2.91 (1.30–6.52)	0.01
Calcification score†						
0	24.3	45.2	1.0	—	1.0	—
1 to 64	24.3	39.7	1.14 (0.49–2.64)	0.76	1.14 (0.43–2.99)	0.92
≥65	51.4	15.1	6.35 (2.35–17.16)	<0.001	10.38 (3.53–30.52)	<0.001
Volume score >75th percentile	41.4	19.1	2.98 (1.41–6.32)	0.004	3.68 (1.62–8.34)	0.002

Values are percentages. *Logistic regression was used for unadjusted odds ratios. For adjusted odds ratios, logistic regression was used after adjustment for Framingham risk score, diabetes, and body mass index; †three classes were created according to the median, which was 65. The first class is 0 that corresponds to absence of calcification, and it is used as the reference level in the logistic regression analyses.
CI = confidence interval; OR = odds ratio.

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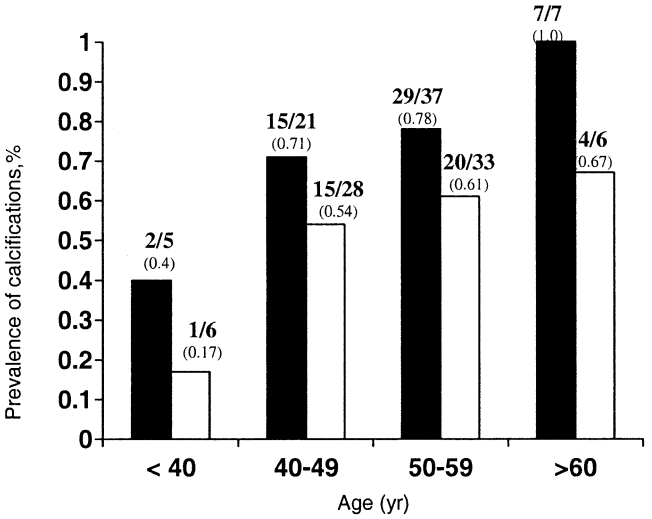

Figure 1. Prevalence of coronary calcification among patients with erectile dysfunction **(black bars)** and control subjects **(white bars)**, according to age.

(16). Several lines of evidence also suggest that atherosclerosis is an inflammatory disease (17), and numerous studies confirmed the independent prognostic relevance of CRP for the risk of CAD, not only in patients with stable or unstable CAD but also in apparently healthy men (18). Erectile dysfunction, therefore, may be considered as the clinical manifestation of a disease affecting penile circulation as a part of a more generalized vascular disorder. Clinical manifestations of vascular diseases rarely appear simultaneously in the same patient. The precise mechanisms by which a specific district is more prone to the development of symptomatic disease are not known. This may occur because of different sizes of various vascular beds. The penis may be a more sensitive vascular bed to systemic disease because of the small diameter of the cavernosal arteries than the larger vessels in the heart. So far, the prevalence of coronary artery atherosclerosis in patients with ED remains unknown because it is difficult to measure noninvasively. In the present study we used MSCT to study subjects with no history of cardiovascular disease, and we found an increased prevalence of CAC among patients with ED independently by traditional risk factors. Thus, to identify asymptomatic patients with ED who are at high risk for cardiovascular events, the use of the Framingham risk score alone is insufficient, and the use of novel markers of risk should be explored. Coronary artery calcification may be such a marker because high calcium score is associated with an increased probability of developing CAD (19).

In conclusion, the present study suggests that ED would represent an early clinical manifestation of a diffuse subclinical vascular disease. We are aware of the limitations of this study, which are the small sample size and the cross-sectional study design; therefore, the conclusions need to be confirmed by other studies. If so, ED should be used together with other cardiovascular risk factors to discriminate patients needing further investigation for subclinical CAD.

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