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Circulation 2004;110;22-26; originally published online Jun 21, 2004;
DOI: 10.1161/01.CIR.0000133278.81226.C9
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Relationship Between Erectile Dysfunction and Silent Myocardial Ischemia in Apparently Uncomplicated Type 2 Diabetic Patients

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Background—Erectile dysfunction (ED) is associated with coronary artery disease (CAD). In diabetic patients, CAD is often silent. Among diabetic patients with silent CAD, the prevalence of ED has never been evaluated. We investigated whether ED is associated with asymptomatic CAD in type 2 diabetic patients.

Methods and Results—We evaluated the prevalence of ED in 133 uncomplicated diabetic men with angiographically verified silent CAD and in 127 diabetic men without myocardial ischemia at exercise ECG, 48-hour ambulatory ECG, and stress echocardiography. The groups were comparable for age and diabetes duration. Patients were screened for ED using the validated International Index of Erectile Function (IIEF-5) questionnaire. The prevalence of ED was significantly higher in patients with than in those without silent CAD (33.8% versus 4.7%; $P=0.000$). Multiple logistic regression analysis showed that ED, apolipoprotein(a) polymorphism, smoking, microalbuminuria, HDL, and LDL were significantly associated with silent CAD; among these risk factors, ED appeared to be the most efficient predictor of silent CAD (OR, 14.8; 95% CI, 3.8 to 56.9).

Conclusions—Our study first shows a strong and independent association between ED and silent CAD in apparently uncomplicated type 2 diabetic patients. If our findings are confirmed, ED may become a potential marker to identify diabetic patients to screen for silent CAD. Moreover, the high prevalence of ED among diabetics with silent CAD suggests the need to perform an exercise ECG before starting a treatment for ED, especially in patients with additional cardiovascular risk factors. **(*Circulation*. 2004;110:22-26.)**

Key Words: coronary disease ■ diabetes mellitus ■ men ■ ischemia, silent myocardial ■ erectile dysfunction

Erectile dysfunction (ED) and atherosclerosis are frequent complications of diabetes.[1–3] Atherosclerosis can play a major role in the development of ED both in the general population and in diabetic patients.[1,2,4–6] An association between overt coronary artery disease (CAD) and ED has been described.[2,5,6] In the diabetic population, the prevalence of silent CAD is particularly high[7,8]; nevertheless, at the present, the prevalence of ED among diabetic subjects with asymptomatic CAD is unknown. Silent CAD is a strong predictor of coronary events and early death, especially in diabetic patients.[9] So, it is of interest to know clinical conditions associated with silent CAD in order to identify subjects to screen for CAD. Moreover, the presence of unknown myocardial ischemia could represent a serious problem in treating ED.[10] This suggests that it may be very useful to understand whether there is an association between ED and silent CAD in diabetic patients; nevertheless, at the present time, no studies have investigated this possible association. The aim of the present study is to evaluate whether ED is associated with asymptomatic CAD in type 2 diabetic patients.

Methods

For this study, we analyzed the male population from two of our previous investigations.[11,12] Population, design, and methods of these studies have been described elsewhere.[11,12] Briefly, in the first investigation,[11] a total of 1323 uncomplicated type 2 diabetic patients without any clinical and electrocardiographic evidence of CAD were consecutively evaluated. Among them, 103 subjects showed an angiographically documented CAD (CAD group). As a control group (NO CAD group), 103 subjects matched by age, gender, and duration of diabetes to CAD patients were recruited. In NO CAD patients, results of exercise ECG, 48-hour ambulatory ECG, and stress echocardiogram were negative for silent myocardial ischemia. In the latter study,[12] a total of 1971 uncomplicated type 2 diabetic patients without clinical signs of cardiovascular diseases and

Received September 30, 2003; de novo received December 21, 2003; revision received March 10, 2004; accepted March 17, 2004.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000133278.81226.C9**

with a negative history of CAD were consecutively evaluated. Among them, patients with electrocardiographic abnormalities suggestive of ischemia or previous asymptomatic myocardial infarction were subjected to a noninvasive test for CAD (ECG stress testing and/or scintigraphy). Among them, 75 patients showed an angiographically documented CAD (CAD group). As a control group (NO CAD group), 75 subjects matched by age, gender, and duration of diabetes to CAD patients were recruited. In NO CAD patients, results of exercise ECG, 48-hour ambulatory ECG, and stress echocardiogram were negative for silent myocardial ischemia.

Out of the total of CAD patients (n=178) recruited into two previous studies,[11,12] 32 were excluded because they were females. As for NO CAD patients, 16 subjects (13 males and 3 females) were used in both previous studies.[11,12] Therefore, out of the total of NO CAD patients (n=162) recruited into two previous studies,[11,12] 29 were excluded because they were females.

From these studies,[11,12] we evaluated the prevalence of ED among 133 uncomplicated type 2 diabetic men with angiographically documented asymptomatic CAD (CAD group) and in a group of 127 type 2 diabetic men without myocardial ischemia at exercise ECG, 48-hour ambulatory ECG, and stress echocardiogram (NO CAD group).

Because screening for ED is a routine analysis in our outpatient department, data on ED were obtained from our database. Screening for ED has been performed by the validated International Index of Erectile Function-5 (IIEF-5) questionnaire.[13] In the present study, we enrolled only male patients screened for ED in the year before the diagnosis of silent CAD or the exclusion of the silent myocardial ischemia.

Among the 133 diabetic patients with angiographically verified silent CAD, 75 derived from the population with normal ECG at rest[11] and 58 derived from the population with ECG abnormalities.[12] Among the 127 NO CAD subjects, 67 derived from the first study,[11] 49 from the latter one,[12] and 11 were used in both previous studies.[11,12] Indeed, 13 CAD patients and 6 NO CAD subjects of the previous studies[11,12] were not enrolled in the present investigation for the following reasons: (1) Data on ED are not available (3 CAD patients and 2 NO CAD subjects); (2) data on ED were collected after the diagnosis of silent CAD or the exclusion of the silent myocardial ischemia (6 CAD patients and 1 NO CAD subject); or (3) data on ED were collected more than 12 months before the diagnosis of silent CAD or the exclusion of the silent myocardial ischemia (4 CAD patients and 3 NO CAD subjects).

Statistical Analysis

By using an analysis of covariance, all data on lipid parameters were adjusted for BMI, smoking, drug intake, presence of hypertension, and microalbuminuria. To assess differences in normal variables the Student's *t* test was utilized. Differences in non-normal variables were assessed by the Mann-Whitney *U* test. The Pearson χ^2 test was exploited for frequency comparison. A multiple logistic regression analysis with the presence of asymptomatic CAD as the dependent variable was performed. Another multiple logistic regression analysis with ED as the dependent variable was performed to identify predictors of ED. Odds ratios (ORs) were estimated and the results were given as ORs and 95% CIs. Data were presented as mean±SD, unless otherwise stated. A value of $P<0.05$ was considered significant.

Results

Table 1 shows clinical and biochemical data of the patients with angiographically detected silent CAD (CAD group) and patients without silent cardiac ischemia (NO CAD group). The percentage of subjects with ED was significantly higher in the CAD than in the NO CAD group.

Among CAD patients, the prevalence of subjects with ED did not differ in the subgroup of subjects with normal resting ECG compared with the subgroup of patients with abnormalities at resting ECG (36.0% versus 31.0%; NS).

TABLE 1. Features of Male Diabetic Patients With and Without Silent CAD

	CAD	NO CAD	*P*
No.	133	127	
Age, y	57.5±6.3	58.2±5.0	0.1477
Duration of diabetes, y	7.1±5.4	7.3±5.3	0.7345
BMI	26.7±3.0	26.1±3.7	0.1553
HbA_{1c}, %	7.4±1.2	7.5±1.3	0.7351
Cholesterol, mmol/L	5.7±1.0	5.4±1.0	0.0313
LDL, mmol/L	3.3±1.1	3.0±1.0	0.0298
HDL, mmol/L	1.1±0.2	1.2±0.2	0.0000
Triglycerides, mmol/L	1.7±0.6	1.6±0.6	0.1476
Microalbuminuria, %	45.1	11.8	0.0000
AER, mg/d			
Mean	55.5±68.6	25.5±40.4	0.0000
Median	25.0	14.0	
Range	5.0–291.0	3.0–258.0	
Smokers, %	59.4	26.0	0.0000
Family history of CAD, %	35.3	29.1	0.2849
Hypertension, %	45.9	54.3	0.1723
Autonomic neuropathy, %	17.3	11.8	0.2110
Lp(a) levels, mg/dL			
Mean	19.7±15.7	15.7±19.6	0.0431
Median	17.5	7.0	
Range	0.5–57.5	0–96.0	
Subjects with at least one isoform of low MW, %	69.2	31.5	0.0000
ED, %	33.8	4.7	0.0000

Lp(a) indicates lipoprotein(a); AER, albumin excretion rate; and MW, molecular weight.

No significant differences in the percentages of subjects treated with thiazide diuretics (12.0% versus 11.0%), β-blockers (6.0% versus 8.7%), or statins (33.8% versus 38.5%) were found between patients with and without silent CAD.

There was no significant difference in the prevalence of subjects with mild to moderate nonproliferative diabetic retinopathy (11.3% versus 9.4%) between patients with and without silent CAD.

A multiple logistic regression analysis was performed with presence/absence of asymptomatic CAD as the dependent variable and the following as predictive variables: age (≥55 versus <55 years[14]), diabetes duration (>10 versus ≤10 years), hypertension (≥130/80 mm Hg or antihypertensive treatment versus <130/80 mm Hg[15]), family history of CAD (documented myocardial ischemia or infarction in a first-degree relative versus no documented myocardial ischemia or infarction in a first-degree relative[14]), smoking (smokers or ex-smokers versus never-smokers), microalbuminuria (albumin excretion rate between 30 and 299 mg/d versus albumin excretion rate <30 mg/d[11,12,15]), HbA_{1c} (≥7.0% versus <7.0%[15]), BMI (≥25 versus <25), lipoprotein(a) (≥30 versus <30 mg/dL[14]), cholesterol (≥200 versus <200 mg/dL[16]), triglycerides (≥150 versus <150 mg/dL[16]), LDL

TABLE 2. Features of Male Diabetic Patients With and Without ED

	ED	NO ED	*P*
No.	51	209	
Age, y	58.8±5.0	57.7±6.9	0.3538
Duration of diabetes, y	8.5±5.3	6.9±5.3	0.0553
BMI	25.6±3.4	26.6±3.3	0.0587
HbA_{1c}, %	7.4±1.1	7.5±1.3	0.8435
Cholesterol, mmol/L	5.5±0.8	5.5±1.0	0.6132
LDL, mmol/L	3.1±0.8	3.2±1.1	0.4194
HDL, mmol/L	1.2±0.2	1.2±0.2	0.4014
Triglycerides, mmol/L	1.7±0.6	1.7±0.6	0.8945
Microalbuminuria, %	66.7	19.7	0.0000
AER, mg/d			
Mean	83.0±83.2	30.5±45.2	0.0000
Median	47.0	15	
Range	6.0–291.0	3.0–268.0	
Smokers, %	47.0	42.1	0.5218
Family history of CAD, %	29.4	33.0	0.6218
Hypertension, %	43.1	51.7	0.2743
Autonomic neuropathy, %	43.1	7.7	0.0000
Lp(a) levels, mg/dL			
Mean	17.9±13.7	18.4±18.7	0.8586
Median	10.5	12.5	
Range	0.5–54.0	0–96.0	
Subjects with at least one isoform of low MW, %	68.6	46.4	0.0044
Silent CAD, %	88.2	42.1	0.0000

Lp(a) indicates lipoprotein(a); AER, albumin excretion rate; and MW, molecular weight.

(≥100 versus <100 mg/dL[16]), HDL (<40 versus ≥40 mg/dL[16]), ED (IIEF-5 scores ≤21 versus >21[13]), apolipoprotein(a) [apo(a)] polymorphism (at least one isoform with molecular weight ≤640 kDa versus only isoforms with molecular weight >640 kDa[11,12,14]), and autonomic dysfunction (abnormal findings in at least one of the 5 standard repeatable tests versus normal findings in all 5 standard repeatable tests[12]). Analysis showed that ED (OR, 14.8; 95% CI, 3.9 to 56.9; $P=0.000$), apo(a) polymorphism (OR, 8.1; 95% CI, 3.4 to 19.0; $P=0.000$), smoking (OR, 4.9; 95% CI, 2.4 to 9.9; $P=0.000$), microalbuminuria (OR, 3.7; 95% CI, 1.6 to 8.8; $P=0.003$), HDL (OR, 3.0; 95% CI, 1.4 to 6.1; $P=0.003$), and LDL (OR, 2.4; 95% CI, 1.0 to 5.4; $P=0.040$) were significant predictors of asymptomatic CAD in diabetic patients. ED appeared to be the most efficient predictor of silent CAD.

Sensitivity, specificity, and positive or negative predictive values have been calculated for ED (sensitivity, 33.8%; specificity, 95.3%; positive predictive value, 88.2%; negative predictive value, 42.1%),

Table 2 shows clinical and biological features of diabetic patients stratified according to the presence/absence of ED. Fifty-one patients had ED; 209 did not have ED. As shown, microalbuminuria, autonomic dysfunction, silent CAD, and low apo(a) phenotypes were significantly higher in subjects with than in those without ED. Diabetes duration was higher in subjects with ED, but it did not attain statistical significance.

No significant differences in the percentages of subjects treated with thiazide diuretics (8.9% versus 12.0%), β-blockers (5.9% versus 7.6%), or statins (31.4% versus 37.3%) were found between patients with and without ED.

There was no significant difference in the prevalence of subjects with mild to moderate nonproliferative diabetic retinopathy (11.8% versus 10.0%) between patients with and without ED.

A multiple logistic regression analysis was performed with presence/absence of ED as the dependent variable and the following as predictive variables: age, diabetes duration, hypertension, family history of CAD, smoking, microalbuminuria, HbA_{1c}, BMI, lipoprotein(a), cholesterol, triglycerides, LDL, HDL, silent CAD, apo(a) polymorphism, and autonomic dysfunction. The logistic regression analysis showed that autonomic dysfunction (OR, 51.1; 95% CI, 12.7 to 205.2; $P=0.000$), silent CAD (OR, 14.0; 95% CI, 3.6 to 55.0; $P=0.000$), and microalbuminuria (OR, 12.3; 95% CI, 4.4 to 34.5; $P=0.000$) were independent predictors of ED in type 2 diabetic patients without clinical signs of CAD. Apo(a) polymorphism did not enter the model.

Discussion

The main finding of this study is that ED seems to be strongly and independently associated with angiographically verified silent CAD in uncomplicated type 2 diabetic patients at relatively low risk for CAD. Indeed, the study population was represented by diabetic subjects without clinical conditions associated with CAD, such as history of artery revascularization, heart failure, uncontrolled hypertension, kidney disease, proteinuria, proliferative retinopathy or previous photocoagulation (used also to treat severe nonproliferative retinopathy and macular edema), previous stroke, or claudicatio intermittens.[11,12]

We found that about one third of patients with silent CAD showed ED, whereas among subjects without silent myocardial ischemia, the prevalence of ED was about 5%. In other words, the prevalence of ED seems to be quite 8-fold higher in patients with than in those without silent myocardial ischemia. In addition, it is interesting to observe that in uncomplicated diabetic patients at relatively low risk of CAD, when there is not silent myocardial ischemia, the prevalence of ED may be even similar to that of the general population.[4,17]

If confirmed, our findings may have some clinical implications in the management of type 2 diabetic patients. First of all, our data suggest that in uncomplicated type 2 diabetic patients at relatively low risk for CAD, ED should be regarded as a potential predictor of silent CAD. At present, American Diabetes Association/American College of Cardiology guidelines recommend noninvasive screening for silent CAD in uncomplicated diabetic patients only when 2 or more common cardiovascular risk factors are present.[18] If our findings are confirmed by other studies, ED should be used together with other cardiovascular risk factors to discriminate

patients needing further investigation for silent CAD. Indeed, in our survey, IIEF-5 questionnaire for screening ED showed good specificity, even if sensitivity was quite low. We also found a high positive predictive value, but it may be overestimated. Indeed, our patients were not population based, but rather selected, so that silent CAD prevalence was about 50%. In a more realistic situation with a silent CAD prevalence of about 10% to 30%,[8] the positive predictive value may be lower than that found in the present study. Nevertheless, the predictive power of the IIEF-5 questionnaire could be increased when used together with other recognized cardiovascular risk factors. Therefore, the IIEF-5 questionnaire should be regarded not only as a simple and reliable tool to screen ED[13] but also a potential tool to assess the global cardiovascular risk profile of diabetic subjects. This appears to be an interesting implication of our study. Indeed, early detection of silent CAD in diabetic patients allows the implementation of specific preventive strategies to reduce mortality and morbidity for coronary events.[18] ED may contribute effectively to the early identification of subjects with silent CAD.

Another implication may pertain to the treatment of ED in uncomplicated diabetic patients. Because specific drug therapies for ED became available, important concerns are arising about their use in patients with ischemic heart disease.[10,19–21] The American College of Cardiology/American Heart Association guidelines recommend that an exercise test should be performed in patients with CAD to identify those at increased risk of myocardial ischemia during sexual intercourse.[10] We found a significant association of ED with silent CAD; this may implicate that uncomplicated type 2 diabetic patients with ED should undergo investigations to exclude silent myocardial ischemia before starting specific drug therapy for ED, especially when other cardiovascular risk factors are present.

It is intriguing to speculate about the possible mechanisms linking ED to silent CAD in diabetic patients. In our study, ED appears to be strongly linked to microalbuminuria, but it is weakly associated with other predictors of coronary atherosclerosis, such as low apo(a) phenotypes.[11,12,14] The strong association of microalbuminuria both with ED and silent CAD suggests that the link between ED and silent CAD may be represented by the endothelial dysfunction. Indeed microalbuminuria is now considered a marker of endothelial dysfunction.[22] In addition, several studies showed that endothelial dysfunction may play a role both in ED and in CAD.[22–24] Another possible mechanism that may explain the relationship between ED and asymptomatic CAD is that both conditions may share a common pattern of cardiovascular risk factors, such as dyslipidemia, hypertension, smoking, and microalbuminuria.[1,4,6,11,12,17,18,20,25]

However, the link between ED and silent CAD may be hypothetically explained by the fact that ED, as a manifestation of autonomic neuropathy, might correlate with the lack of symptoms in diabetic patients with CAD. Indeed, in diabetic patients autonomic neuropathy has been found associated not only with ED[2,26] but also with asymptomatic CAD.[27] Specific investigations on the possible relationship between ED and symptomatic CAD in diabetic patients may clarify this issue. Several studies found an association between ED and overt CAD both in type 1 and type 2 diabetic subjects.[2,26,28,29] An association of ED with known CAD has been described also in the general population.[4–6,25] One study has even suggested a correlation between ED and CAD severity.[6] However, in the these studies the clinical presentations of CAD often were not described; therefore, a clear association between ED and symptoms of CAD is not documented. Nonetheless, data from the literature clearly suggest that ED is independently correlated with overt CAD; thus, it is likely that there may be also a correlation between ED and asymptomatic CAD independent of autonomic neuropathy, as suggested by the present study. Nevertheless, the hypothesis that ED, as a manifestation of autonomic neuropathy, may be linked with the lack of symptoms in a proportion of diabetic patients with silent CAD cannot be excluded.

Still, central nervous system may offer another intriguing link between ED and silent CAD; indeed, the involvement of the central nervous system has been suggested both in the pathways of afferent pain signals from myocardium[30] and in the central mechanisms of erectile dysfunction,[31] especially in hypogonadism,[32] which is a frequent condition in type 2 diabetic patients.[33]

Further studies are still needed to better investigate the possible common background underlying the relationship between ED and silent CAD in diabetic patients.

The present study might have some limitations. First, we have evaluated patients recruited into previous studies; those studies were not specifically designed to investigate the relationships between ED and silent CAD.[11,12] Nonetheless, our choice to evaluate only patients with data on ED collected in the 1 year before the diagnosis of silent CAD or the exclusion of myocardial ischemia should eliminate any bias. Indeed, in this way, the assessment of sexual activity is close to the evaluation of the presence/absence of silent myocardial ischemia. In addition, in the present study, no differences in age, diabetes duration, and glycemic control were found between diabetic patients with and without silent myocardial ischemia. Therefore, age, diabetes duration, and glycemic control cannot influence data on ED and the relationships between ED and silent CAD. Another potential limitation may be the fact that the study population derives from two different investigations. However, it is important to remember that the prevalence of ED did not differ significantly in the subgroup of CAD patients with normal resting ECG (derived from the first study[11]) compared with that of CAD patients with abnormal ECG at rest (derived from the latter study[12]).

In conclusion, the present study suggests that ED appears to be strongly and independently associated with silent CAD in apparently uncomplicated type 2 diabetic patients. If our finding is confirmed by further studies, ED may be used as a potential predictor of silent CAD among diabetic patients. In addition, the high prevalence of ED among patients with silent CAD suggests the usefulness of an exercise ECG before starting a treatment for ED, especially in patients with additional cardiovascular risk factors.

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