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ORIGINAL ARTICLE

Erectile dysfunction and angiographic extent of coronary artery disease in type II diabetic patients

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Some studies observed an association between erectile dysfunction (ED) and coronary artery disease (CAD) extent in the general population, but others did not. There are no specific studies in diabetic populations. The aim of the present study was to evaluate whether ED is correlated with the extent of angiographic CAD in a large group of type II diabetic patients. We recruited 198 consecutive type II diabetic males undergoing an elective coronary angiography to evaluate chest pain or suspected CAD. Presence and degree of ED were assessed by the International Index Erectile Function – 5 (IIEF-5) questionnaire. ED was considered present, when IIEF-5 score was $\leqslant 21$. Moreover, each domain of IIEF-5 was considered. Angiographic CAD extent was expressed both by the number of vessels diseased and by the Gensini scoring system. The percentage of subjects with ED was significantly higher (45.8 versus 15.8%; $P = 0.0120$) in patients with ($n = 179$) than in those without ($n = 19$) significant angiographic CAD (stenosis of the lumen $\geqslant 50\%$). No significant association of CAD extent with presence of ED, total IIEF-5 score and each domain of IIEF-5 was observed. Our study shows that ED was significantly more prevalent in type II diabetic males with angiographic CAD than in those with normal arteries. However, no correlation was found between the extent of angiographic CAD and the presence or the severity of ED.
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Introduction

Coronary atherosclerosis is earlier, more frequent and more accelerated in diabetic than in non-diabetic subjects. The rapid and diffuse progression of coronary atherosclerosis in diabetic patients may be due to diabetes *per se*, but also to other associated cardiovascular risk factors, such as hypertension, dyslipidemia, visceral obesity. Nevertheless, these conventional cardiovascular risk factors explain only partially this increased cardiovascular risk in diabetic patients.[1] In addition, there are no suitable markers to identify diabetic patients with a more severe coronary artery disease (CAD). These markers may be hypothetically useful in clinical practice to discriminate patients at higher risk for severe CAD in order to implement specific preventive, diagnostic and therapeutic programs.

There is growing evidence that erectile dysfunction (ED) is strongly associated with the presence of overt and silent CAD in both diabetic and non-diabetic patients.[2–4] Some studies evaluated whether ED could be a marker of CAD severity in the general population, but the results were quite conflicting.[5–7] To the best of our knowledge, there are no specific studies in diabetic populations. Studies evaluating the relationship between ED and CAD extent in the general population[5–7] verified the relationship between ED and CAD extent also in subgroups of diabetic patients. Nevertheless, these subgroups were quite small. In addition, diabetic populations were not well characterized, since several important factors that could significantly

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influence CAD extent were not taken into account (metabolic control, type of diabetes, diabetes duration, microalbuminuria, associated complications). For all these reasons, we designed a specific study in a well-characterized large diabetic population.

The aim of the present study was to evaluate whether the presence and the severity of ED are correlated with the extent of angiographic CAD in type II diabetic patients.

Methods

Patients

The study population consisted of 198 consecutive type II diabetic males undergoing an elective coronary angiography to evaluate chest pain or suspected CAD. Patients with a personal history of CAD (namely with an already established diagnosis of CAD) were excluded. Other exclusion criteria were: age <40 or >70 years, duration of diabetes <12 months, cardiomyopathy, heart failure, history of artery revascularization, renal insufficiency (serum creatinine $\geqslant 130\,\mu$mol/l), proteinuria (dipstick-positive proteinuria or albumin excretion rate (AER) $\geqslant 300$ mg/day), alcoholism, neoplasia, liver and endocrine diseases. All patients gave their informed consent to participate in the study.

Diabetes was diagnosed according to the American Diabetes Association criteria.[8] Hypertension was diagnosed according to the European Society of Hypertension/European Society of Cardiology criteria[9] or in presence of a specific treatment. Patients with AER <30 mg/day were considered normoalbuminuric; patients with AER between 30 and 299 mg/day were considered microalbuminuric. Patients were considered smokers if current smokers or ex-smokers. Family history of CAD was considered positive in presence of a documented myocardial ischemia or infarction in a first-degree relative. Body mass index (BMI) was calculated by the following formula: kg/m^2.

ED assessment

The presence and the degree of ED were assessed by the validated International Index Erectile Function – 5 (IIEF-5) questionnaire.[10] ED was considered present, when IIEF-5 score was $\leqslant 21$.[10] Each domain of IIEF-5 was evaluated. Only patients who filled in the IIEF-5 questionnaire in the 2 years before the angiography were enrolled. The questionnaire was filled in 9.3 ± 5.6 months (range: 1–23 months) before the procedure.

Laboratory procedures. Venous blood samples were taken from subjects after fasting for 12 h. Cholesterol, HDL and triglycerides were measured by an automatic analyser HITACHI 737 (Tokio-Japan). LDL was calculated by Friedewald's formula. Glycated haemoglobin (HbAlc) was measured by high-performance liquid chromatography (BioRad, Richmond, CA, USA). AER was measured by nephelometry (Beckmann, Milan, Italy).

Severity of CAD. All patients enrolled in the study were subjected to coronary angiography, performed using the Sones technique with filming of multiple views of each vessel. Significant CAD was considered present, when a stenosis of at least 50% of the lumen was found in a major coronary vessel. The 198 diabetic patients were divided into four subgroups on the basis of stenotic major coronary arteries. Moreover, the results of quantitative coronary angiography have also been expressed according to the Gensini scoring system.[11] The Gensini score was computed for each patient by assigning the severity score to each coronary stenosis in accordance with the degree of the vessel narrowing and its geographic importance. Reductions in the diameter of the lumen of 25, 50, 75, 90, 99% and complete occlusion were attributed to Gensini score of 1, 2, 4, 8, 16 and 32, respectively. To each principal vascular segment, a multiplier, according to the functional significance of the myocardial area supplied by this segment, was assigned: the left main coronary artery, $\times 5$; the proximal segment of the left anterior descending coronary artery, $\times 2.5$; the proximal segment of the circumflex artery, $\times 2.5$; the mid-segment of the left anterior descending coronary artery, $\times 1.5$; the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, $\times 1.5$ and others, $\times 0.5$. So, the Gensini score = sum of (stenosis score $\times$ functional significance score). Patients with significant coronary disease were also subdivided into two subgroups with a Gensini score $\leqslant 40$ or with a Gensini score >40. In patients who have undergone PTCA or aorto-coronary by-pass surgery, the angiographic severity was measured before the revascularization procedures.

Statistical analysis. By using an analysis of covariance, all data regarding lipid parameters were adjusted for sex, BMI, smoking, drug intake, presence of hypertension, microalbuminuria. To assess differences in cholesterol, LDL, HDL, BMI, the analysis of variance was utilized. Owig to the the highly 'skewed' distribution of triglycerides levels, to compare triglycerides values, the Kruskall–Wallis test was used. The Pearson χ^2 test was exploited for frequency comparison. Linear regression analysis was performed to evaluate the relation between degree of ED and CAD severity. A multiple logistic regression analysis was performed with CAD severity (Gensini score $\leqslant 40$ or >40) as the dependent

variable and the following as predictive variables: age ($\geqslant 55$ versus <55 years), diabetes duration (>10 versus $\leqslant 10$ years), hypertension ($>130/80$ mmHg or antihypertensive treatment versus $<130/80$ mmHg), 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), smoking (smokers or ex-smokers versus never-smokers), microalbuminuria (albumin excretion rate between 30 and 299 mg/day versus albumin excretion rate <30 mg/day), HbAlc ($\geqslant 7.0$ versus $<7.0\%$), BMI ($\geqslant 25$ versus <25), cholesterol ($\geqslant 200$ versus <200 mg/dl), triglycerides ($\geqslant 150$ versus <150 mg/dl), LDL ($\geqslant 100$ versus <100 mg/dl), HDL (<40 versus $\geqslant 40$ mg/dl), ED (IIEF-5 score $\leqslant 21$ versus IIEF-5 score >21). Odds Ratios (ORs) were estimated and the results were given as ORs and 95% CI. In addition, a forward multiple regression analysis with the presence of CAD severity (Gensini score as a continuous variable) as the dependent variable was performed. In this analysis, the variables were tested as continuous ones. Non-normal variables, such as triglycerides, were log-transformed before the analysis. The following were tested as potential predictors: age, diabetes duration, systolic and diastolic blood pressure, family history of CAD, smoking, albumin excretion rate, HbAlc, BMI, cholesterol, triglycerides, LDL, HD, IIEF-5 score. Data were presented as means$\pm$s.d., unless otherwise stated. $P<0.05$ was considered significant.

Results

Diabetic patients were divided into four subgroups on the basis of stenotic major coronary arteries: 19 patients showed normal coronary arteries, 56 a single-vessel disease, 46 a two-vessel disease and 77 a three-vessel disease. Table 1 reports the features of the whole study population and of patients stratified by the number of vessels diseased and by Gensini score (patients with a Gensini score $\leqslant 40$ and those with a Gensini score >40). As shown, subgroups were comparable for age, diabetes duration and glycemic control. No significant differences were found in the percentage of subjects with ED and in IIEF-5 score among the subgroups with 0, 1, 2, and 3 vessels diseased. Nevertheless, the percentage of subjects with ED was significantly higher (45.8 versus 15.8%; $P=0.0120$) in patients with ($n=179$) than in those without ($n=19$) significant angiographic CAD. Among 80 patients with hypertension, five were treated with hypodic diet alone and 75 with at least one antihypertensive drug. A total of 52 patients were treated with ACE inhibitors, 43 with Angiotensin Receptor Blockers, 31 with calcium antagonists, 12 with beta-blockers, six with diuretics, five with clonidine and four with doxazosine. In Table 1, only the percentages of patients treated with diuretics and beta-blockers are reported, since these drugs may promote ED.

No significant difference in IIEF-5 score was found among the subgroups of patients with normal arteries, with a Gensini score $\leqslant 40$ and those with a Gensini score >40. Presence of ED was significantly correlated with the increasing extent of the coronary atherosclerosis. Nevertheless, when only patients with significant angiographic CAD were considered, no significant differences in the percentage of subjects with ED (48.0 versus 42.9%; $P=0.4909$) and in IIEF-5 scores (20.0 ± 5.8 versus 20.8 ± 5.1; $P=0.5455$) were found between patients with a Gensini score >40 ($n=102$) and those with a Gensini score $\leqslant 40$ ($n=77$).

In the whole population, no significant correlation was found between the total IIEF-5 score and CAD extent, as assessed both by the number of coronary vessels diseased ($r=0.016$; $P=0.813$) and by Gensini score ($r=-0.070$; $P=0.321$). No significant correlation was found between each domain of IIEF-5 and CAD extent.

Multivariate analysis. A multiple logistic regression analysis showed that cholesterol (OR: 3.54; 95% CI: 1.53–8.15; $P=0.003$) and family history of CAD (OR: 2.53; 95% CI: 1.26–5.08; $P=0.009$) were significant predictors of CAD severity in diabetic patients. ED did not enter the model ($P=0.303$). We repeated the multivariate analysis by using a forward stepwise regression analysis. Analysis showed that only total cholesterol ($\beta=0.020$; $P=0.003$) was significant predictor of CAD severity in diabetic patients. IIEF-5 did not enter the model ($P=0.798$). Multivariate analysis was repeated by including each domain of IIEF-5 and not the total IIEF-5 score to the list of potential predictors. No domain of IIEF-5 did enter the model. In addition, considering the higher percentage of subjects with ED among patients with one- and two-vessel disease, we repeated all multivariate analyses in this subgroup. No significant association of CAD extent with total IIEF-5 score and each domain of IIEF-5 was observed.

Discussion

The present study shows that presence and degree of ED are not independently correlated with the angiographic extent of CAD. Indeed, the prevalence of ED does not differ significantly in subgroups of patients stratified by the number of vessels diseased. The prevalence of ED significantly correlated with the increasing extent of the coronary atherosclerosis in subgroups with normal arteries, with Gensini score $\leqslant 40$ and with Gensini score >40. Nevertheless, among patients with significant angiographic CAD, no significant difference in ED prevalence was

Table 1 Clinical and biological features of the whole study population and of subgroups with 0, single-, two-, and multi-vessel stenosis and of subgroups with CAD patients with Gensini score $\leqslant 40$ and those with Gensini score >40

	Total	*No stenosis*	*Single-vessel*	*Two-vessel stenosis*	*Multi-vessel stenosis*	P[a]	*Gensini score* $\leqslant 40$	*Gensini score* >40	P[b]
N	198	19	56	46	77		77	102	
Age (years)	57.8±6.6	57.5±6.4	57.3±7.0	58.9±6.5	57.5±6.3	NS	57.9±6.8	57.7±6.5	NS
Family history for CAD (%)	28.8	10.5	17.9	26.1	42.9	<0.01	26.0	34.3	NS
Hypertension (%)	40.4	42.1	32.1	45.6	42.9	NS	35.1	44.1	NS
BMI	26.3±3.1	26.6±4.4	25.2±2.4	27.2±3.0	26.6±2.9	<0.01	25.7±2.5	26.7±3.1	NS
Diabetes duration (years)	7.5±5.7	6.7±4.2	7.5±5.6	7.5±6.3	7.7±6.0	NS	7.7±6.2	7.3±5.6	NS
HbAlc (%)	7.5±1.7	7.2±1.3	8.0±2.2	7.2±1.3	7.5±1.5	NS	7.7±2.1	7.3±1.3	NS
Microalbuminuria (%)	38.9	10.5	44.6	52.2	33.8	<0.01	44.2	40.2	<0.05
Smoking (%)	67.7	36.8	67.8	73.9	71.4	<0.05	74.0	68.6	<0.01
Cholesterol (mmol/l)	5.9±1.1	5.2±0.5	5.7±0.9	6.2±1.2	6.0±1.1	0.001	5.7±1.0	6.1±1.2	0.001
LDL (mmol/l)	3.8±1.0	3.3±0.6	3.6±0.8	4.1±1.1	3.9±1.1	<0.01	3.7±0.9	4.0±1.2	<0.01
HDL (mmol/l)	1.2±0.3	1.2±0.1	1.1±0.3	1.2±0.3	1.2±0.4	NS	1.1±0.3	1.2±0.3	NS
Triglycerides (mmol/l)	1.9±0.9	1.7±0.5	2.0±1.1	1.8±0.7	1.9±0.9	NS	2.0±1.0	2.0±1.3	NS
Diuretics (%)	3.0	0	1.8	6.5	2.6	NS	2.6	3.9	NS
Beta-blockers (%)	6.0	5.3	5.4	6.5	6.5	NS	3.9	7.8	NS
Statins (%)	31.8	31.6	37.5	28.3	29.9	NS	36.3	28.4	NS
ED (%)	42.9	15.8	46.43	52.2	41.6	NS	42.8	48.0	<0.05
Total IIEF-5 score	20.4±5.6	21.4±6.0	20.3±5.7	19.3±6.0	20.9±5.0	NS	20.6±5.3	20.0±5.7	NS
Domain #1	4.0±1.3	4.4±1.2	4.0±1.5	3.9±1.3	4.1±1.3	NS	4.1±1.2	3.9±1.3	NS
Domain #2	4.0±1.2	4.3±1.2	4.1±1.2	3.8±1.4	4.1±1.1	NS	4.1±1.1	3.9±1.3	NS
Domain #3	4.1±1.2	4.3±1.4	4.1±1.1	4.0±1.3	4.3±1.1	NS	4.1±1.1	4.1±1.2	NS
Domain #4	4.1±1.3	4.3±1.3	4.1±1.3	3.8±1.5	4.1±1.2	NS	4.1±1.3	4.0±1.3	NS
Domain #5	4.1±1.5	4.2±1.5	4.1±1.3	3.9±1.3	4.3±1.1	NS	4.2±1.1	4.1±1.3	NS

[a]Statistical significance among patients with no stenosis, single-, two-, and multi-vessel stenosis.
[b]Statistical significance among patients with no stenosis, with Gensini score $\leqslant 40$ and with Gensini score >40.
NS: not significant.

observed. In addition, no correlation was found between IIEF-5 score and angiographic CAD severity, as assessed both by the number of vessels diseased and by the Gensini score. At last, multivariate analyses did not show any independent association of ED and IIEF-5 with CAD extent.

To avoid confounding factors, we recruited only patients with ED assessment performed before the angiography and with a negative history of CAD. This appears to be important, since ED assessment was not influenced by the presence of cardiovascular events.[12] In addition the exclusion of patients with known CAD may be important since in these patients treatments for CAD, including revascularization, can affect coronary atherosclerosis progression and thus the possible association between CAD extent and the variables tested. In addition, in our study, we have considered drugs that can affect CAD severity, such as statins, and the development of ED, such as diuretics and beta-blockers. The prevalence of these drug classes did not differ significantly among subgroups of patients stratified both by the number of vessels diseased and by Gensini score. So drug intake does not seem to influence our findings. Moreover, also the prevalence of subjects with hypertension did not show any significant difference among the subgroups. This is another important point, considering that hypertension is potentially associated with ED. So, to explain the lack of association between ED and CAD extent in our survey, it is intriguing to hypothesize that in diabetic patients the progression of coronary atherosclerosis starts before the development of diabetes itself and ED. The early and rapid progression of CAD before the development of hyperglycemia and ED could be due to insulin resistance.[13] Insulin resistance usually begins many years before the development of type II diabetes mellitus.[13] Insulin resistance is a powerful independent cardiovascular risk factor[13] and can promote atherosclerosis independently of the presence of diabetes.[14] Thus, in insulin-resistant subjects, the development of diabetes and ED could further increase the risk for CAD progression; nevertheless, ED does not appear to be able to discriminate those diabetic patients who already have a more severe CAD. However, to test this intriguing hypothesis, longitudinal studies are needed.

In the general population, the relationship between ED and CAD extent are conflicting.[5–7] Indeed, Greenstein suggested an association between ED and CAD severity.[5] Solomon *et al*.[6] confirmed this association. Nevertheless, in a large group of CAD patients, Montorsi *et al*.[7] did not find any relationship between CAD angiographically assessed and ED. These conflicting results may be due to several reasons. Differences in ED assessment, in the definition of angiographically significant stenosis and in the prevalence of diabetic patients among the

studies, may explain at least partially their conflicting results.

An interesting finding of our study is that the group of diabetic patients with normal arteries shows a prevalence of ED significantly lower than that found in patients who developed CAD. The relatively small number of patients with normal arteries at angiography does not permit a reliable multivariate analysis to ascertain the independent predictive value of ED for CAD. Nevertheless, we hypothesize that ED may predict the future development of CAD angiographically verified in type II diabetic patients, since in our survey ED was assessed before the angiographic evaluation of CAD. ED may be related to autonomic neuropathy that may also promote the development of CAD. Nevertheless, this hypothesis has to be evaluated by specific large prospective studies.

In conclusion, our study shows that ED was significantly more prevalent in type II diabetic males with angiographic CAD than in those with normal arteries. However, no significant correlation was found between the extent of angiographic CAD and the presence and severity of ED.

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