Cardiorenal Determinants of Erectile Dysfunction in Primary Prevention: A Cross-Sectional Study

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Significance of the Study

- In this study, left ventricular hypertrophy and kidney dysfunction were independent risk factors for severe erectile dysfunction (ED). However, the significance of carotid plaques or total cardiovascular risk was not confirmed. Hence, the presence of ED could be associated with not only vascular function, but also chronic myocardial injury, such as hypertrophy, or kidney dysfunction. Therefore, ED could be a marker for cardiovascular disease and indicate the need to take preventive measures.

Abstract

Objective: The aim of this study was to investigate the association between the severity of erectile dysfunction (ED), cardiovascular risk, and target organ damage (heart, renal, vascular) in men free of cardiovascular diseases (CVD). **Subjects and Methods:** ED was assessed using the International Index of Erectile Function (IIEF-5). The study included 182 men: 100 with ED (IIEF mean score ≤21) and 82 without ED (IIEF mean score >21). Ultrasound was used to evaluate carotid plaques and left ventricular mass, geometry, and diastolic function. Cardiovascular anamnesis, CVD risk factors, and anthropo-metric and biochemical parameters were obtained. The European Society of Cardiology-Systematic Coronary Risk Evaluation Score (ESC-SCORE) was used to calculate total patient cardiovascular risk. Continuous variables between groups were compared using the Student t test and Mann-Whitney U test, while categorical data were compared using the χ^2 test. Multiple linear regression was used to test the association between the severity of ED and presence of target organ damage. **Results:** The following parameters were significantly higher in the ED group compared to the controls: family history of coronary heart disease (43.7 vs. 26.7%, $p = 0.047$), ESC-SCORE (2.27 ± 1.79 vs. 1.61 ± 1.13, $p = 0.012$), and waist circumference (109.28 ± 10.82 vs. 106.17 ± 10.07, $p = 0.047$). Impaired renal function ($p = 0.081$), albuminuria ($p = 0.545$), vascular damage ($p = 0.602$), and diastolic function ($p = 0.724$) were similar in both groups. However, left ventricular hypertrophy (LVH; odds ratio 2.231, 95% CI 1.069–

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4.655, p = 0.22) was more frequent in the ED group (29.9 vs. 16.0%). The multiple linear regression analysis revealed that LVH (β = 1.761, p = 0.002) and impaired renal function assessed using the estimated glomerular filtration rate (<60 mL/min/1.73 m^2; β = 6.207, p = 0.0001) were the independent risk factors for severity of ED. ***Conclusion:*** This study showed that LVH and impaired renal function are associated with ED severity.

Introduction

Erectile dysfunction (ED) is a clinical marker of a vascular disease in high-risk patients. Risk factors for ED include hypertension [1], diabetes mellitus [2], cardiovascular disease (CVD) [3], metabolic syndrome (MS) [4], tobacco use [5], hyperlipidemia [6], hypogonadism [7], lower urinary tract symptoms [8], and depression [9]. However, the multiethnic study of atherosclerosis (MESA) showed ED to be an independent predictor of CVD events [10].

Left ventricular hypertrophy (LVH) is associated with increased risk of major cardiovascular events and all-cause mortality; it may also be an independent predictor of morbid cardiovascular events [11]. Renal dysfunction, either defined by urine albumin excretion or estimated glomerular filtration rate (eGFR), or both, also predicts a heightened cardiovascular risk [12, 13]. All these conditions are associated with diabetes [14], myocardial infarction [15], hypercholesterolemia [16], valvar stenotic and regurgitate lesions [17], as well as African American ethnicity [18].

The temporal relationship between subclinical CVD that may precede overt clinical CVD and target organ damage by longer than a decade, and the onset of ED remains poorly described [12–17]. Therefore, in this study, the goal was to evaluate which parameters of target organ damage or subclinical vascular disease had the strongest relationship with ED severity.

Subjects and Methods

Study Participants

The study was conducted at the Outpatient Preventive Cardiology Clinic, Vilnius University Hospital Santaros Klinikos, Lithuania. The study population consisted of 182 Caucasian primary prevention subjects. The inclusion criteria were the presence of cardiovascular risk factors, and the ability to read and understand
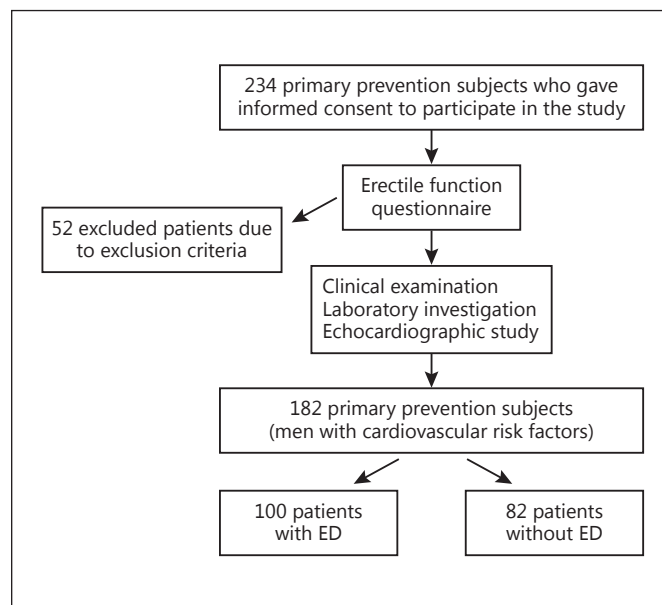

Fig. 1. Flow chart of the study population.

the study and the associated questions (Fig. 1). Patients either married or currently in a stable relationship with a partner and who were sexually active were enrolled in this study.

Written informed consent was obtained from all participants and the protocol was approved by the Institutional Review Board. Demographic data were collected from the patients, as well as a complete medical, surgical, and psychosexual history. A detailed physical examination and biochemical tests were performed. The International Index of Erectile Function (IIEF) questionnaire was used to evaluate erectile function. Participants were assigned to either of the 2 study groups based on their IIEF scores.

Study Design

In this cross-sectional study all measurements were performed in the morning between 8:00 and 11:00 a.m. Participants were requested to abstain from tobacco, coffee, and food for at least 12 h. Any vasoactive medication intake was to be discontinued for at least 24 h before the study.

Height in meters, weight in kilograms, and waist circumference in centimeters were measured. Waist circumference was measured with a measuring tape at the midpoint between the bottom of the rib cage and the top of the iliac crest, in a standing position, with the subject breathing normally. The body mass index was also calculated (as kg/m^2).

Blood pressure (BP) measurements were performed with subjects in a seated position following a 10-min resting period. Two consecutive measurements of BP and heart rate were obtained and the average of the 2 measurements was recorded.

Information about traditional cardiovascular risk factors was collected from patient anamnesis, physical examination, and medical history. Hypertension was defined as any systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or a history of antihypertensive medication use. Current smoking was defined as any cigarette smoking during the past month.

Table 1. Baseline characteristics of the patients

	ED+ (n = 100)	ED– (n = 82)	p value
IIEF score	18.30±2.91	23.41±1.04	0.0001*
Age, years	47.28±3.96	46.33±4.37	0.132
BMI	31.96±4.49	30.79±4.07	0.068
WC, cm	109.28±10.82	106.17±10.07	0.047*
ESC-SCORE	2.27±1.79	1.61±1.13	0.012*
Systolic BP, mm Hg	138.78±13.58	135.68±13.51	0.145
Diastolic BP, mm Hg	88.91±9.29	87.48±9.17	0.321
MAP, mm Hg	105.33±10.43	102.64±10.70	0.151
Fasting glucose, mmol/L	6.26±1.29	6.28±1.75	0.954
Total cholesterol, mmol	6.39±1.52	6.36±1.22	0.896
LDL cholesterol, mmol/L	3.99±1.38	3.98±1.11	0.973
HDL cholesterol, mmol/L	1.22±1.21	1.16±0.29	0.605
TG, mmol/L	3.10±3.13	2.61±1.92	0.192
CRP, mg/L	3.21±3.09	3.71±7.39	0.572
Urine albumin, mg/L	19.64±65.15	15.33±39.40	0.637
Urine creatinine, mmol/L	13.38±5.32	14.47±6.40	0.290
ACR	1.38±3.75	1.05±2.58	0.555
Serum creatinine, μmol/L	79.70±12.69	81.02±10.73	0.516
eGFR, mL/min/1.73m^2	86.99±8.13	88.24±4.87	0.285

Data are presented as the mean ± SD. ED+, with erectile dysfunction; ED–, control group without erectile dysfunction; IIEF, International Index of Erectile Function; BMI, body mass index; WC, waist circumference; CV, cardiovascular; ESC-SCORE, the European Society of Cardiology-Systematic Coronary Risk Evaluation Score; BP, blood pressure; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; CRP, C-reactive protein; ACR, albumin to creatinine ration; eGFR, glomerular filtration rate.

The diagnosis of MS was based on the 2005 modified criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). Three or more of the following factors had to be present: hypertension ≥140 mm Hg, waist circumference ≥102 cm, serum triglycerides (TG) ≥1.7 mmol/L, high-density lipoprotein cholesterol <1 mmol/L, and fasting glucose ≥5.6 mmol/L.

International Index of Erectile Function

Patients were screened for the presence of ED using the validated IIEF questionnaire. A score <21 (out of a total of 25 points) was used as a threshold value for the diagnosis of ED. At this cut-off point the test has a sensitivity of 98 and a specificity of 88% [19]. The analysis focused on 2 groups: patients with an IIEF-5 score >21 (without ED, the control group) and with an IIEF-5 score ≤21 (the ED group).

Echocardiographic Examination

Echocardiography was performed with participants lying in a supine position and turned to their left side at a 30° angle. An echocardiography machine with a 2.5-MHz transducer (GE Systems, Oslo, Norway) was used to obtain 2-dimensional guided M-Mode echocardiograms at chord level just below the mitral valves. Septal and posterior wall thickness as well as left ventricular chamber dimensions were measured following the American Society of Echocardiography (ASE) guidelines. The left ventricle mass index (LVMI) was calculated using the ASE-recommended formula:

$$LVMI\ (g/m^2) = (1.04\ [(IVST + LVID + PWT)^3 - LVID^3] - 13.6)/body\ surface\ area,$$

where IVST is the interventricular septal thickness, LVID is the left ventricle internal dimension, and PWT is the posterior wall thickness.

LVH is defined as LVMI ≥95 g/m^2 in females and ≥115 g/m^2 in males. Diastolic dysfunction was evaluated by septal and lateral E, and the left atrial volume according to the EAE/ASE Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography [20].

Fasting glucose and lipids (total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-C], and TG), C-reactive protein, as well as serum creatinine were measured using the Cobas 8,000 modular analyzer series (Roche Diagnostics, Vienna, Austria). Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = TC – HDL-C – TG/2.2. The eGFR was calculated from the serum creatinine level standardized to an isotope dilution mass spectrometry using the chronic kidney disease epidemiology collaboration equation [21]. The urine albumin to creatinine ratio (ACR) was calculated in milligrams of albumin per millimole of creatinine (mg/mmol). Kidney damage was considered present with ACR ≥3 and a decreased GFR with eGFR <60 mL/min/1.73 m^2.

Table 2. Values of target organ damage markers according to ED

	ED+ (n = 86)	ED– (n = 82)	p value
Kidney dysfunction (eGFR <60)	5.8 (5)	0	0.081
ACR ≥3	1.16 (1)	0	0.545
Plaques in carotid arteries (total score)	45.34 (39)	39.03 (32)	0.306
ABI <0.9	4.65 (4)	3.65 (3)	0.586
LVH ≥115 g/m^2	29.01 (29)	15.85 (13)	0.022
Diastolic dysfunction	21 (18)	23.2 (19)	0.431

Data are presented as % (n). ED+, with erectile dysfunction; ED–, control group without erectile dysfunction; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; ABI, ankle brachial index; LVH, left ventriclular hypertrophy.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 16.0 (version for Windows). Values of quantitative variables were expressed as frequencies or means ± standard deviation (SD).

Differences between the ED groups were tested using the Student t test for normally distributed variables and the Mann-Whitney U test for abnormally distributed continuous variables, while categorical data were compared using the χ^2 test. The Pearson correlation was used to associate target organ damage parameters with the IIEF score.

Forward stepwise models of linear multiple regression were used to test the association between the severity of ED and impaired renal function (eGFR <60 mL/min/1.73 m^2), albuminuria (ACR ≥3), diastolic dysfunction, carotid plaques, LVH, and MS as independent variables. In all tests, a p value <0.05 was statistically significant.

Multiple linear regression analysis models were used to evaluate possible independent risk factors influencing the severity of ED. The multivariate model consisted of the IIEF score as the dependent variable, and impaired renal function (eGFR <90 mL/min per 1.73 m^2), albuminuria (ACR ≥3), diastolic dysfunction, carotid plaques, LVH, and MS as independent variables.

Results

The mean age of the population was 47.5 ± 3.4 years. Of the 182 patients, ED was diagnosed as mild in 79 (43.4%), mild to moderate in 17 (9.3%), moderate in 3 (1.6%), and severe 1 (0.5%). Men with ED had a significantly higher cardiovascular risk and prevalence of family history of coronary heart disease than those in the control group. No significant differences were found regarding smoking, diabetes mellitus, obesity, duration of obesity, MS, or hypertension between the ED patients and controls. The baseline features of both groups are presented in Table 1.

Values of target organ damage markers were similar in both groups except for LVH (29 [29.9%] in the ED group

vs. 13 [16.0%] in the control group, p = 0.022; Table 2). The odds ratio for LVH was 2.231 (95% CI 1.069–4.655, p = 0.022) in the ED group.

Univariate analysis showed a significant isolated association between the IIEF score and ACR (r = –0.149, p = 0.015) and left ventricular myocardial mass index (r = –0.139, p = 0.008). No association was found between the IIEF score and carotid plaques (r = –0.057, p = 0.516), eGFR (r = –0.021, p = 0.815), MS (r = 0.0408, p = 0.543), or ankle brachial index (r = –0.07, p = 0.516).

The echocardiographic parameters are summarized in Table 3. No significant difference was observed between the groups regarding diastolic dysfunction (21.0% [n = 21] in the ED group vs. 23.2% [n = 19] in the control group, p = 0.724). Only the E/E'septal ratio was significantly different between the groups (11.45 ± 3.45 in the ED group vs. 10.24 ± 3.50 in the control group, p = 0.046). When all variables were assessed concurrently for influencing ED severity, only LVH (β = 1.761, p = 0.002) and impaired renal function (β = 6.207, p = 0.0001) were identified as independent predictors (Table 4).

Discussion

In this study, the severity of ED was associated with LVH and impaired renal function. The finding that ED was associated with ventricular hypertrophy confirmed the study of Kakkavas et al. [22] in which it was reported that ED was associated with left ventricular diastolic dysfunction, which is an early abnormality in the evolution of hypertensive LVH. Heikkilä et al. [23] found a U-shaped correlation between ED and diastolic BP, which confirms the link between ED and severity of hypertension. ED and hypertension share a common pathogenesis, namely vas-

Table 3. Echocardiography variables related to ED

	ED+ (n = 100)	ED− (n = 82)	p value
Cardiac chamber diameters			
Aorta, cm	3.36±0.36	3.25±0.34	0.060
Left atrium, cm	3.97±0.43	3.92±0.43	0.521
Left atrial index, cm/m^2	1.84±0.19	1.79±0.20	0.173
Left atrial volume, mL	69.08±19.00	65.44±13.55	0.197
Left atrial volume index, mL/m^2	32.26±8.88	29.79±5.84	0.054
LVSD, cm	3.31±0.48	3.35±0.48	0.727
LVDD, cm	5.23±0.47	5.15±0.48	0.334
Left ventricular index, cm/m^2	2.42±0.21	2.36±0.28	0.130
Right ventricle, cm	2.71±0.32	2.63±0.30	0.166
LVEF, %	54.93±0.58	54.92±0.64	0.892
Left ventricular hypertrophy			
RWT	0.45±0.30	0.40±0.06	0.189
Septum thickness in systole, cm	1.47±0.25	1.42±0.24	0.397
Septum thickness in diastole, cm	1.09±0.11	1.04±0.14	0.021*
PWT in systole, cm	1.52±0.29	1.45±0.28	0.323
PWT in diastole, cm	2.51±12.31	1.03±0.14	0.307
LVMI, g/m^2	102.42±20.50	94.93±21.67	0.02*
LAVI, mL/m^2	32.26±8.88	29.79±5.84	0.054
Diastolic function			
E wave velocity, m/s	0.78±0.15	0.76±0.18	0.425
A wave velocity, m/s	0.74±0.13	0.70±0.15	0.145
E wave deceleration time, m/s	246.09±99.97	242.30±97.85	0.824
E/A ratio, m	1.09±0.30	1.11±0.32	0.621
E'lat wave velocity, m/s	10.45±2.79	11.10±3.12	0.213
A'lat wave velocity, m/s	10.33±2.18	10.90±3.18	0.242
E/E'lat ratio	7.67±2.52	7.35±2.80	0.489
E/E'mean ratio	2.56±3.10	2.85±3.06	0.592
E'septal wave velocity, m/s	7.2±1.79	7.8±1.83	0.385
A'septal wave velocity, m/s	10.02±2.27	9.64±2.14	0.319
E/E'septal ratio	11.45±3.45	10.24±3.50	0.046*
IVRT, m/s	98.32±21.89	95.13±19.80	0.409

ED+, with erectile dysfunction; ED−, without erectile dysfunction; LVSD, left ventricular systolic diameter; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; LAVI, left atrial volume index; E, mitral inflow early diastolic velocity; A, mitral inflow late diastolic velocity; E'lat wave velocity, lateral annular early diastolic velocity by tissue Doppler imaging; A'lat wave velocity, lateral annular late diastolic velocity by tissue Doppler imaging; E'septal wave velocity, septal annular early diastolic velocity by tissue Doppler imaging; A'septal wave velocity, septal annular late diastolic velocity by tissue Doppler imaging; IVRT, isovolumetric relaxation time.

cular disease, with the penile vasculature a particularly sensitive marker of systemic disease. The specific mechanism is thought to be due to increased levels of angiotensin II, which contributes to systemic hypertension and has been demonstrated in the corporal blood of hypertensive rats. Increased angiotensin II levels cause a subsequent increase in reactive oxygen species, which in turn reduces nitric oxide levels via a scavenging mechanism [24].

It is now well known that CKD is a risk factor for CVD [25]. Endothelial dysfunction is an early marker of CVD, and it has also been reported to occur in CKD patients [26, 27]. In addition, endothelial dysfunction is a cause of ED, because nitric oxide production from the endothelium decreases in this state. Therefore, it is not surprising that ED frequently occurs in CKD patients. Furthermore, consistent with our patients (all with MS), CKD patients

Table 4. Multiple linear regression analysis with IIEF score as the dependent variable and LVH, MS, diastolic dysfunction, impaired renal function, albuminuria (ACR ≥3), and carotid plaques as independent variables

Model term	Coefficient	SE	T	Significance	95% CI		Importance
					lower	upper	
Intercept	13.179	1.663	7.926	0.0001	9.898	16.460	
LVH	1.761	0.566	3.113	0.002	0.645	2.878	0.399
eGFR <60 mL/min/1.73 m^2	6.207	1.626	3.818	0.0001	0.299	9.415	0.601

LVH, left ventricle hypertrophy; MS, metabolic syndrome; eGFR, estimated glomerular filtration rate; SE, standard error.

often suffer from metabolic diseases such as hypertension, hyperlipidemia, and impaired fasting glucose. These metabolic abnormalities also cause endothelial dysfunction and are risk factors for ED as well as CVD. Therefore, in addition to the concomitant metabolic diseases, CKD per se appears, at least in some part, to cause ED via the induction of endothelial dysfunction.

The limitations of this study were the lack of penile duplex Doppler ultrasonography, at least in patients with ED based on the IIEF. Also, testosterone serum concentrations were not measured.

Conclusions

In this study, the presence of ED was associated with chronic myocardial injury, such as hypertrophy, or impaired renal function, indicating that ED is a probable marker of CVD and the need to take preventive measures towards it. Hence, patients with ED are advised to undergo both urological and cardiovascular examinations to improve not only their sexual health, but also their overall health and survival.

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