ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Is Erectile Dysfunction a Reliable Proxy of General Male Health Status? The Case for the International Index of Erectile Function—Erectile Function Domain

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ABSTRACT

Introduction. Erectile dysfunction (ED) has emerged progressively as a sentinel marker of cardiovascular disease (CVD). The correlation between ED and the burden arising from multiple comorbid conditions has been incompletely analyzed.

Aim. Assess whether erectile function, defined with the International Index of Erectile Function–Erectile Function (IIEF-EF) domain score, is associated with health-significant comorbidities scored with the Charlson comorbidity index (CCI).

Methods. Clinical and hemodynamic variables of the last 140 consecutive patients who underwent penile color Doppler ultrasonography for new-onset ED were considered. Patients were assessed with a thorough medical and sexual history. Health-significant comorbidities were scored with the CCI.

Main Outcome Measure. Descriptive statistics and either linear or logistic regression models tested the association among IIEF-EF, hemodynamic parameters, and CCI, which was included in the model both as continuous and categorized variable (0 vs. ≥1).

Results. Complete data were available for 138 patients (98.6%) (mean age 46.6 years [standard deviation 13.0]; range 21–75 years). CCI was 0, 1, and ≥2 in 94 (68.1%), 23 (16.7%), and 21 (15.25%) patients, respectively. Of all, 35 patients (79.5%) did not have a CVD comorbidity. Mean IIEF-EF was 13.7 (9.3). ED severity was no ED, mild, mild to moderate, moderate, and severe in 12 (9.1%), 28 (20.2%), 12 (9.1%), 23 (16.2%), and 63 (45.5%) patients, respectively. At multivariable linear regression analysis, CCI significantly worsened with increased age ($\beta = 0.33$; $P = 0.001$) and decreased IIEF-EF values ($\beta = -0.25$; $P = 0.01$). At logistic regression analysis, age (odds ratio [OR]: 1.05; $P = 0.004$) and IIEF-EF (OR: 0.95; $P = 0.04$) emerged as significant predictors of categorized CCI.

Conclusions. Severity of ED, as objectively interpreted with IIEF-EF, accounts for a higher CCI, which may be considered a reliable proxy of a lower general male health status regardless of the etiology of ED. **Salonia A, Castagna G, Saccà A, Ferrari M, Capitanio U, Castiglione F, Rocchini L, Briganti A, Rigatti P, and Montorsi F. Is erectile dysfunction a reliable proxy of general male health status? The case for the International Index of Erectile Function—Erectile function domain. J Sex Med 2012;9:2708–2715.**

Key Words. Erectile Dysfunction; Erectile Function; International Index of Erectile Function; Comorbidities; Health Status

Introduction

Sexual health is a cornerstone aspect of overall health for both genders [1,2]. Data suggested that sexual health declines, while concomitant morbidities increase among European men as a function of age [3]. More specifically, the older that men get, the more they become affected above all by hypertension, obesity, and heart disease; likewise, throughout their aging process, men start

dealing with erectile dysfunction (ED) and severe orgasmic impairment, both closely associated with concomitant comorbidities [3]. In this context, ED has progressively emerged as an important sentinel marker of men's overall health, assuming major relevance in the cardiovascular field [4–9]. This is particularly important in individuals with diabetes mellitus [10–15].

ED may significantly increase the risk of cardiovascular disease (CVD), coronary heart disease, stroke, overall atherosclerotic cardiovascular events [16], and all-cause mortality [4–9], and the increase is probably even independent of conventional cardiovascular risk factors [5,17], glycometabolic control, and ED severity [18,19].

Considering the importance of these findings, a comprehensive history along with a physical examination should become routine practice for sexual medicine specialists treating men with ED not just to investigate and study sexual health per se but, *quoad vitam*, to also evaluate the cardiovascular health profile of these men [11,17,20,21]. Recommending to the general practitioner to screen every man with an initial presentation of ED for standard cardiovascular risk factors and whenever necessary, to start cardioprotective interventions should also become a common practice [10,22,23].

It has been also demonstrated that ED is linked to different comorbid conditions and overall poorer male health [24–30]. The situation is further complicated by the fact that exactly because they are comorbidities, each comorbid disease can affect general health status, eventually having a negative impact on individual sexual health [31]. Overall, we fully endorse the idea of Corona et al. [32] and support the concept that ED represents an opportunity to screen for the presence of concomitant morbidities.

In this direction, we sought whether impaired ED per se, as objectively defined by the International Index of Erectile Function–Erectile Function (IIEF-EF) domain score [33,34], is associated with health-significant comorbidities, as scored with the Charlson comorbidity index (CCI) [35], in a cohort of consecutive Caucasian European heterosexual men complaining of new-onset ED as their primary sexual disorder.

Methods

Patients

From May 2010, clinical and ultrasound variables of the last 140 consecutive Caucasian European heterosexual men who underwent dynamic penile color Doppler ultrasonography for new-onset ED of broad-spectrum etiology at the same academic outpatient clinic were considered for this analysis. Patients were assessed with a thorough medical history, including data on health-significant comorbidities as scored with the CCI [35], which is the most extensively studied hospital-based comorbidity index used by health researchers in their effort to measure comorbid disease status or case mix in health-care databases. Its original version contains 17 different disease comorbidity categories, each allocated a weight of 1–6 based on the adjusted relative risk of 1-year mortality and summed to provide a total score; the higher the score, the more severe the burden of comorbidity [35]. As a consequence, CCI sum is an indicator of disease burden and a strong estimator of mortality [35]. We used the *International Classification of Diseases*, 9th revision, Clinical Modification (ICD-9-CM) because its coding algorithms were used to define the 17 comorbidities that constitute the most widely used CCI. Measured body mass index (BMI), defined as weight in kilograms by height in square meters, was considered for each patient. For BMI, we used the cutoffs proposed by the National Institutes of Health [36]: normal weight (18.5–24.9), overweight (25.0–29.9), class 1 obesity (30.0–34.9), and class ≥2 obesity (≥35).

To provide a frame of reference for objectively interpreting ED severity, we used the IIEF-EF score [33] categorized according to the classification proposed by Cappelleri et al. [34]. For the specific aim of this study, we also considered the duration of ED before seeking medical help (number of months).

Symptoms of late-onset hypogonadism were not specifically collected for this cohort of men.

Dynamic penile color Doppler ultrasonography, using an intracavernosal injection of prostaglandin E1 (PGE$_1$) (20 mcg) plus audiovisual and manual genital stimulation, was performed in all patients to assess penile hemodynamics. The test was conducted by three expert technicians (i.e., each performing >50 evaluations per year) according to the protocol previously reported by Montorsi et al. [37] with the specific purpose to obtain an erection comparable with the maximal physiological erection (that is the erection obtained at home during sexual activity). In this context, cavernosal peak systolic velocity (PSV), resistance index (RI), and acceleration (ACC). were bilaterally evaluated 20 minutes after intracavernosal PGE$_1$ injection [37].

Literacy problems as well as other reading and writing problems were excluded in all patients.

Our institution's ethics committee approved the study, and all patients signed an informed consent agreeing to deliver their own anonymous information for future studies.

According to the specific aims of the study, patients for whom a detailed medical history was not evaluable (N = 2; 1.4%) were excluded from the analysis. Thus, the present analyses were based on 138 assessable patients (98.6%).

Main Outcome Measures

The primary end point of the present study was to assess whether severity of ED, as objectively interpreted with the IIEF-EF, is associated with health-significant comorbidities, as scored with the CCI. The secondary end point was to assess whether overall men's health, as scored with the CCI, was associated with any ultrasound variables.

Statistical Analyses

Data are presented as mean (median; range). Spearman correlation analysis tested the association between IIEF-EF and predictors. Univariable (UVA) and multivariable (MVA) linear and logistic regression models tested the association between clinical and ultrasound variables and CCI. The CCI was included in the model either as a continuous or a categorized variable (0 vs. ≥ 1). Statistical analyses were performed using S-Plus Professional, v.1 (MathSoft, Inc., Seattle, WA, USA). All tests were two-sided, with a significance level set at 0.05.

Results

Table 1 lists patient demographic characteristics and descriptive statistics. Overall, obesity was found in 18 (13%) of the whole cohort of patients. Of 138 patients, 44 (31.8%) had a CCI ≥ 1. According to IIEF-EF segregation, 126 patients (91.3%) had ED. Mean IIEF–sexual desire domain score was 6.4 (median: 7.0), IIEF–intercourse satisfaction domain scored 6.1 (median: 7.0), IIEF–orgasmic function domain scored 6.2 (median: 6.8), whereas IIEF–overall satisfaction domain scored 4.8 (median: 4.0). Table 2 details the comorbidities according to their diagnostic categories and the ICD-9-CM codes. At Spearman correlation analysis, IIEF-EF was inversely associated with age ($r = -0.35$; $P = 0.0004$), continuously coded CCI ($r = -0.22$; $P = 0.02$), duration of ED ($r = -0.29$; $P = 0.004$), and positively associated

Table 1 Patients characteristics and descriptive statistics (N = 138)

Age (years)	
Mean (median)	46.6 (44)
Range	21–75
BMI (kg/m²)	
Mean (median)	26.0 (25.5)
Range	16.0–42.0
BMI (No. [%])	
Normal weight	59 (42.8)
Overweight	61 (44.2)
Class 1 obesity	8 (5.8)
Class ≥ 2 obesity	10 (7.2)
CCI score	
Mean (median)	0.7 (0.0)
Range	0–5
CCI (No. [%])	
Score 0	94 (68.1)
Score 1	23 (16.7)
Score ≥ 2	21 (15.2)
Relationship status (No. [%])	
No stable sexual relationship	41 (29.7)
Stable sexual relationship ≥ 12 months	97 (70.3)
IIEF-EF score	
Mean (median)	13.7 (12.0)
ED severity (No. [%])	
No ED	12 (9.1)
Mild	28 (20.2)
Mild-to-moderate	12 (9.1)
Moderate	23 (16.2)
Severe	63 (45.5)
ED duration (months)	
Mean (median)	44.4 (24.0)
Range	12–360

BMI = body mass index; CCI = Charlson comorbidity index; IIEF-EF = International Index of Erectile Function–Erectile Function domain; ED = erectile dysfunction

with mean RI ($r = 0.23$; $P = 0.02$) and mean ACC time ($r = 0.35$; $P = 0.001$). Conversely, no clear association emerged with BMI ($r = 0.06$; $P = 0.52$) and mean PSV value ($r = 0.12$; $P = 0.23$).

At UVA linear regression analysis, continuously coded CCI increased with age, whereas CCI was inversely associated with IIEF-EF and ACC times (all, $P \leq 0.03$) (Table 3). In contrast, no clear association emerged at UVA between BMI, ED duration, PSV or RI values, and CCI (Table 3). Similarly, at MVA linear regression analysis, age and IIEF-EF emerged as independent predictors of continuously coded CCI (all, $P \leq 0.01$) (Table 3). Similarly, ACC times (all, $P \leq 0.03$) were inversely associated with CCI (Table 3). No clear association was found between continuously coded CCI and all the other variables at MVA linear regression analysis (Table 3).

At UVA logistic regression analysis, categorized CCI increased with age but significantly decreased with increased IIEF-EF scores (all, $P \leq 0.04$) (Table 4). In contrast, no clear association emerged at UVA logistic regression between CCI

Table 2 Diagnostic categories, ICD-9-CM Codes, and CCI weights within the whole cohort (No. [%])

Condition	ICD-9-CM codes	CCI weights	(No. [%])
Acute myocardial infarction			
Old myocardial infarction	412	1	4 (2.9)
Congestive heart failure			
Congestive heart disease	428	1	3 (2.2)
Peripheral vascular disease			
Aortic aneurysm	441	1	1 (0.7)
Peripheral vascular disease NOS	443.9	1	1 (0.7)
Pulmonary disease			
Chronic bronchitis	491	1	1 (0.7)
Emphysema	492	1	2 (1.4)
Bronchiectasis	494	1	1 (0.7)
Connective tissue disorder			
Polymyositis	710.4	1	1 (0.7)
Rheumatoid arthritis	714	1	2 (1.4)
Peptic ulcer			
Peptic ulcer NOS	533	1	1 (0.7)
Liver disease			
Chronic hepatitis	571.4	1	2 (1.4)
Diabetes			
Diabetes mellitus	250	1	4 (2.9)
Diabetes complications			
With renal manifestations	250.4	2	2 (1.4)
Renal disease			
Nephritis and nephropathy	583	2	1 (0.7)
Cancer (malignant neoplasm)			
of the fundus of stomach	151.3	2	1 (0.7)
of the descending colon	153.2	2	1 (0.7)
of the rectosigmoid junction	154.0	2	1 (0.7)
of the anal canal	154.2	2	1 (0.7)
of the main bronchus	162.2	2	1 (0.7)
of the trigone of the bladder	188.0	2	1 (0.7)
of the lateral wall of the bladder	188.2	2	2 (1.4)
of the kidney	189.0	2	1 (0.7)
Hodgkin disease	201	2	1 (0.7)
Lymphoma NOS	202.8	2	1 (0.7)
Other causes of myelitis	323.82	2	1 (0.7)
Multiple sclerosis	340	2	4 (2.9)
Metastatic cancer			
Testis cancer with positive retroperitoneal lymph nodes	196.2	3	1 (0.7)
HIV disease	0.42	6	1 (0.7)

ICD = International Classification of Diseases; CCI = Charlson comorbidity index; NOS = not otherwise specified; HIV = human immunodeficiency virus

and all the other variables (Table 4). Similarly, at MVA logistic regression analysis, age and IIEF-EF emerged as independent predictors of categorized CCI (all, $P \leq 0.04$) (Table 4). Conversely, no clear association was found between categorized CCI and all the other variables at MVA logistic regression analysis (Table 4).

Discussion

We tested whether severity of ED, as objectively assessed through a validated, widely available psychometric tool, may be considered a reliable proxy of overall men's health as scored with the CCI in a relatively small cohort of consecutive Caucasian European heterosexual men complaining of new-onset ED as their primary sexual disorder. Our findings show that CCI worsened with increased

Table 3 Univariable and multivariable linear regression models predicting CCI (as continuously coded)

	Univariable analysis		Multivariable analysis	
Predictor	Beta	*P* value	Beta	*P* value
Age	0.54	0.001	0.33	0.001
BMI	0.31	0.9	0.25	0.8
ED duration	−0.05	0.2	−0.07	0.5
IIEF-EF	−0.25	0.03	−0.25	0.01
PSV 20′ right	−0.08	0.41	−0.09	0.39
PSV 20′ left	−0.008	0.5	−0.16	0.1
PSV 20′ mean value	−0.14	0.1	−0.16	0.2
RI 20′ right	−1.04	0.5	−0.19	0.06
RI 20′ left	−0.16	0.09	−0.17	0.08
RI 20′ mean value	−0.19	0.06	−0.21	0.07
ACC right	−0.001	0.01	−0.25	0.02
ACC left	−0.001	0.03	−0.24	0.03
ACC mean value	−0.28	0.01	−0.26	0.01

CCI = Charlson comorbidity index; BMI = body mass index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function–Erectile Function domain; PSV = peak systolic velocity; RI = resistance index; ACC = acceleration

Table 4 Univariable and multivariable logistic regression models predicting CCI (as categorized, 0, ≥1)

Predictor	Univariable analysis		Multivariable analysis	
	OR	*P* value	OR	*P* value
Age	1.05	0.004	1.04	0.04
BMI	1.03	0.24	1.02	0.45
ED duration	0.96	0.46	0.93	0.20
IIEF-EF	0.95	0.04	0.96	0.03
PSV 20′ right	0.98	0.11	0.99	0.48
PSV 20′ left	0.98	0.21	1.00	0.94
PSV 20′ mean value	0.98	0.1	1.00	0.80
RI 20′ right	0.28	0.33	0.70	0.89
RI 20′ left	0.31	0.40	1.35	0.91
RI 20′ mean value	0.27	0.35	0.92	0.96
ACC right	0.99	0.06	0.99	0.43
ACC left	0.99	0.17	1.00	0.72
ACC mean value	0.99	0.08	0.99	0.42

CCI = Charlson comorbidity index; BMI = body mass index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-Erectile Function domain; PSV = peak systolic velocity; RI = resistance index; ACC = acceleration; OR = odds ratio

age and increased ED severity, as depicted for decreased IIEF-EF scores.

Current results confirm previous observations that men with CVD and overall atherosclerotic cardiovascular events frequently experience ED [4,5,8,17,38,39], thus supporting the concept that ED may play the role of a sentinel marker of men's cardiovascular health [5–11,16,18,19,21,40,41]. Indeed, in our cohort, of 44 patients with CCI ≥1, 9 (20.5%) had a CVD of any form. However, our analysis was original exactly when it showed that the severity of ED was significantly associated with comorbid conditions other than CVD, among them diabetes mellitus, respiratory disorders, connective tissue disorders, kidney and liver impairment, neurological diseases, and several cancers. More specifically, both the linear and the logistic regression analyses concerning our own cohort of men further supported the idea that ED severity may be linked with a lower level of general health regardless of patient age, with CCI sum as a widely recognized indicator of disease burden and a strong estimator of mortality [35]. Even more translationally important, IIEF-EF emerged as a potential proxy of overall male health status. From the everyday clinical practice standpoint, these findings prompt us to further outline the importance of taking a comprehensive medical and sexual history and performing a thorough physical examination in all men with ED [6,10,11,17, 19,20,23,42]. In other words, this new evidence would suggest that if a patient complains of severe ED, one could already affirm that individual may also have other comorbid conditions, and

consequently, that man may warrant a more comprehensive medical assessment, regardless of his age [30,41,43]. In this sense, we fully agree with Corona et al. [32] supporting the concept that ED may ultimately represent an opportunity to screen for the presence of concomitant morbidities. Conversely, it will be possible to infer that patients with a significant burden of comorbid diseases can also have a severe form of ED [44], deserving adequate attention in terms of sexual health and quality of life.

A major strength of this analysis emerges from the possibility of retrieving most of this information by simply using the EF domain of the IIEF questionnaire, whose 15 questions still remain the most important tool to unify the goals of researchers and to be able to help or criticize every new acquisition in the field of ED, trying to overcome the infinite limits of subjectivity. This correlation between the burden of comorbidities and ED severity emerges as an almost new acquisition because previous examples only correlated single comorbidities with the degree of erectile function impairment [45].

One feature of our study is that it was a single-institute survey with a relatively small cohort of consecutive homogeneous, same-race heterosexual patients for whom medical and sexual evaluation was performed in a consistent manner in the real-life setting. A further strength is that the patients included in this study presented a wide variety of ED etiologies, possibly allowing for adequate variability in the psychometric and hemodynamic parameters to provide a robust analysis.

As expected, the correlation analyses suggested that ED severity was related with patients' age, with this finding clearly confirming most of the previously published data [3,46–48]. The latter observation certainly corroborates the validity of our cohort of men as a representative sample of broad-spectrum etiologies of ED patients, along with the expected finding that ED severity could increase along with ED duration [49], burden of comorbid conditions [24,25,46–48], RI, and ACC times at the dynamic penile color Doppler ultrasonography assessment [50,51]. Conversely, these data did not confirm previous findings concerning a strong correlation between PSV values and ED severity [50,51], but our relatively small cohort of patients could probably justify such a discrepancy.

Our study is not devoid of limitations. The study reports the results of an exploratory analysis that may be optimal for this cohort of same-race

heterosexual men, but that would deserve external validation with an independent larger sample and, possibly, with men from different countries or ethnic backgrounds. In this context, although the study has provided absolutely original results when it showed that the severity of ED was significantly associated with comorbid conditions other than CVD, this cohort was certainly too small to perform a multivariate analysis further separating those individuals with CCI ≥1 in different subcategories, thus excluding exactly those patients with a medical history positive for CVDs. Moreover, we lacked data about the potential impact that drugs, either taken individually or together for various comorbid conditions, may eventually have on erectile functioning. Indeed, there are data suggesting that the number of medications a man takes is associated with worse ED even after comorbidities have been taken into account [6,38,39,52]. Similarly, our analyses did not take into consideration cigarette smoking and other recreational habits that had been already clearly associated with ED of various degrees of severity, with data also suggesting a potential interaction with the patient's medical history [46,48,53,54]. Additional research with external validation is thus needed to confirm these results.

Conclusions

This study provides novel evidence that the severity of ED, as objectively interpreted with IIEF-EF, accounts for a higher CCI, which may be considered a reliable proxy of lower male general health status, regardless of the etiology of ED. In practical terms, these findings prompt us to further outline the importance of taking a comprehensive medical and sexual history, and performing a thorough physical examination in all men with ED regardless of their age. Because the current sample size is limited, we cannot derive general conclusions; therefore, additional studies in larger population-based samples are needed to confirm these results and to further characterize the potential role of ED severity as a harbinger of medical disorders in some men.

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