

## ORIGINAL ARTICLE

# Psychological features in men with erectile dysfunction with or without preclinical atherosclerosis

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Psychological distress was assessed with a multidimensional self-report questionnaire (Symptom Check-List-90R) in 247 men complaining of erectile dysfunction (ED), with or without preclinical atherosclerosis. This was estimated by ultrasound determination of intima-media thickness (IMT) in common carotid arteries (CC). Psychological distress was reported in 31% of men and was more prevalent in those with a vascular damage. A higher level of obsessive–compulsive (OC) features was observed in men with high CC-IMT ( $P=0.0069$ ; OR 3.18, CL 1.31–7.80). Among a large number of vascular risk factors, elevated CC-IMT and a severe ED resulted independently associated with an elevated level of OC features (OR 3.36, CL 1.38–8.15; OR 2.60, CL 1.01–6.70, respectively). Mental stress driven by OC features may link ED and vascular disease by activating reciprocal exacerbating mechanisms. Psychological distress identifies men at risk for cardiovascular disease that deserve a vigorous treatment of ED to reduce risk of vascular events.

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## Introduction

Ancillary studies showed little relationship between sexual dysfunctions and psychiatric disorders,<sup>1,2</sup> while more recent studies documented psychiatric disorders in a large number of men who sought consultation for erectile dysfunction (ED), ranging between 37%<sup>3</sup> and 63.1%.<sup>4</sup> Population-based cross-sectional surveys on middle-aged and elderly individuals based on self-administered questionnaires have confirmed the predictive role of depressive symptoms or of diagnosed depression on ED.<sup>5–8</sup> Prospective results from the Massachusetts Male Aging Study have shown that the presence of

untreated depressive symptoms in healthy middle-aged men is not a risk for incident ED, while a personality trait of dominance is protective for incident ED.<sup>9</sup> A recent prospective 5-year study in Finnish men demonstrated that only treated depression but not untreated depressive mood at baseline increased the risk of incident ED, while the presence of ED at baseline increased the risk for incident depressive mood.<sup>10</sup> Therefore, psychological features may represent independent risk factors for ED, while depressive mood might be a consequence<sup>9,10</sup> or a coexisting condition of ED.<sup>9</sup> Psychological features and psychiatric disorders are also significantly associated to incident coronary heart disease (CHD).<sup>11–13</sup> The strong association of ED and preclinical atherosclerosis,<sup>14,15</sup> and between ED and psychological distress<sup>3,4</sup> prompted us to analyze whether self-reported symptoms of psychological distress are differentially expressed in men with ED with or without preclinical atherosclerosis. The aim was to challenge the speculation that some psychological features, explored by a self-rated instrument, may be added to the list of ED correlates.

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## Methods

### *Study design*

Two hundred and forty-seven consecutive men aged 30–77 years presented to the Andrology outpatient clinic of the University of L'Aquila General Hospital because of primary ED for more than 12 months were enrolled. The Sexual Health Inventory for Men (SHIM)<sup>16</sup> evaluated the erectile function. Scoring the SHIM allowed a classification of each patient as having no (25–20) or mild to total (19–0) ED. Exclusion criteria were absence of a stable heterosexual relationship in the last 12 months, a female partner with severe chronic disease including psychiatric diseases, an ongoing divorce or death of a partner in the last 12 months, relevant job or family problems in the last 12 months. Exclusion criteria were also moderate or heavy alcohol consumption (more than 500 ml of wine and one drink of spirit per day on average), weekly use of recreational drugs, history of endocrine diseases other than diabetes, pelvic surgery or trauma, prostate diseases, penile curvature, neurological or overt psychiatric diseases, CHD, stroke and other overt vascular diseases such as angina abdominis and intermittent claudication. A self-administered multicomponent questionnaire explored medical conditions, smoking was also recorded and smokers were considered all men with current and/or past smoking, without considering a minimum period to define the patient as a current or past smoker. Enrolled ED men were requested to sign an informed consent and entered the study approved by the local ethic committee. Fifty-nine patients ( $42.52 \pm 12.2$  years) were in good health, and were not exposed to vascular risk factors (VRFs). One hundred and eighty-eight patients ( $51.5 \pm 10.8$  years) were exposed to VRFs including overweight (body mass index  $> 25 \text{ kg/m}^2$ ), hyperlipidemia, diabetes and essential hypertension.

### *Blood measurements*

Venous blood samples for determination of plasma fasting glucose, serum c-reactive protein (CRP), low-density lipoproteins (LDL), high-density lipoprotein (HDL) and total testosterone were determined with standard procedures and commercial kits.

### *Ultrasonographic determinations of vascular damage*

Ultrasound thickness of common carotid arteries intima-media layer (CC-IMT), a well-accepted prognostic indicator of early atherosclerosis,<sup>17</sup> was evaluated in all patients as a marker of vascular damage in large arteries. A CC-IMT  $\geq 0.9 \text{ mm}$  is associated to an increased risk of cardiovascular events over a follow-up of 6 years in elderly people

without clinical cardiovascular disease,<sup>17</sup> suggesting that it may be an evidence of preclinical vascular damage. A Doppler spectrum analysis of cavernous arteries was also used to evaluate arterial damage in the penis. CC-IMT determination and Doppler spectrum analysis of cavernous arteries were performed as reported,<sup>18,19</sup> with a duplex scanner equipped with color flow imaging (HDI 3000, ATL Diagnostic Ultrasound System) and a 10-MHz linear array transducer.

### *Assessment of psychological features*

All participants were asked to complete the Symptom Check-List-90R (SCL-90R),<sup>2,20</sup> a multidimensional symptom self-report inventory composed of 90 items, and each rated on a five-point scale of distress, from 0 (not at all) to 4 (extremely). The instrument is scored on nine primary symptom dimensions: somatization, obsessive-compulsive (OC), interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The dimensional structure of the SCL-90-R has been confirmed<sup>20</sup> and it resulted to be sensitive to the psychological distress associated with sexual dysfunction.<sup>2</sup> The test was administered to patients by an experienced investigator who remained available to answer any question that the patients might ask.

### *Statistical analysis*

Clinical and laboratory data are presented as median (interquartile range). Psychological distress was defined as the presence of at least one of nine subscale indexes higher than the 90th percentile. Differences of percentages were assessed by  $\chi^2$ -test, and by two sample tests of proportions as indicated, while differences of clinical and laboratory data were assessed by Wilcoxon rank-sum test, after assessing the non-normal distribution of data (Shapiro-Wilk test). A multivariate logistic analysis with stepwise selection was performed to evaluate the association between an elevated level each of nine psychological dimensions as outcome variables and a large number of co-variables. These included type 2 diabetes, essential arterial hypertension, hyperlipidemia, smoke, age  $> 65$  years, CC-IMT indicative for a vascular damage ( $\geq 0.9 \text{ mm}$ ), severe ED (SHIM score  $\leq 9$ ), measures of each VRFs significantly associated to an increased risk for vascular diseases. Cut-off values of VRFs included BMI  $> 25 \text{ kg/m}^2$ ,<sup>21</sup> fasting glucose level  $> 5.7 \text{ mmol/l}$ ,<sup>22</sup> LDL-c level  $> 3.37 \text{ mmol/l}$ ,<sup>23</sup> CRP level  $> 5000 \mu\text{g/l}$ .<sup>24</sup> Level of total testosterone was also included in the analysis and a cut-off value  $< 8.66 \text{ nmol/l}$  was indicative for a low total testosterone level.<sup>25</sup> Both the confidence intervals for the regression parameters and the

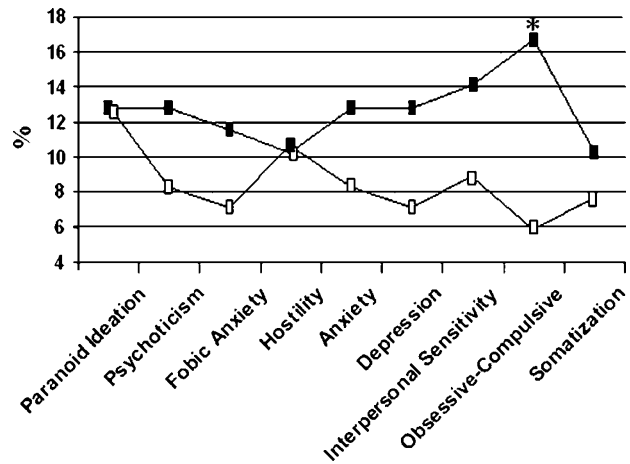
confidence intervals of ORs were estimated using the profile likelihood function. All statistical analyses were performed using SAS/Statistical software (Statistical Analysis System Institute, Inc., Rel. 8, 2000, Cary, NC, USA).

## Results

According to ultrasonographic determination of CC-IMT, 79 patients (32%) showed a CC-IMT  $\geq 0.9$  mm, corresponding to the 75th percentile in the study group. Men with CC-IMT  $\geq 0.9$  mm showed a significantly lower SHIM score, higher age and body mass index (BMI), as well as higher blood level of CRP and of fasting glucose (Table 1). No differences were observed in the school education between the two groups.

SCL-90-R symptom profile distribution in the study group showed 77 patients (31%) with a subscale index higher than the 90th percentile of one or more psychological dimensions. Men with CC-IMT  $\geq 0.9$  mm showed a relatively higher percentage of cases with high level of interpersonal sensitivity, phobic anxiety, depression, somatization, anxiety, psychoticism and a significantly higher percentage of cases with high level of OC dimension ( $P=0.0069$ ; OR: 2.83, CL 95%: 1.14–7.15 after controlling for age, BMI, blood level of CRP and of fasting glucose, and for SHIM score) (Figure 1). The difference in percentage of men with high level of OC dimension between groups with or without a vascular damage remained significant after controlling, in a bivariate analysis, for each of

nine psychological dimensions of SCL-90-R. A multivariate logistic analysis with stepwise selection was then performed to evaluate the association between an elevated level of each of nine psychological dimensions as outcome variables and a large number of predictor co-variables listed in the Statistical Analysis section. A significant association was found only between an elevated level of OC features and a CC-IMT indicative for a vascular damage, or a severe ED (SHIM score  $\leq 9$ ). The two co-variables resulted independently associated to an elevated level of OC features (CC-IMT  $\geq 0.9$  mm: OR 3.36, CL



**Figure 1** Percentage of men with ED with a score value each of nine psychological items greater than the 90th centile. ■ indicates men with CC-IMT  $\geq 0.09$  cm; □ indicates men with CC-IMT  $< 0.09$  cm. \* $P=0.0069$ ; OR: 2.83, CL 95%: 1.14–7.15 after controlling for age, BMI, SHIM score, CRP level and fasting glucose level.

**Table 1** Clinical characteristics in men with ED associated or not associated to a CC-IMT indicative for preclinical atherosclerosis ( $\geq 0.9$  mm)

Variables	IMT $< 0.9$ mm (n = 168)	IMT $\geq 0.9$ mm (n = 79)	P <sup>a</sup>
SHIM score	15.00 (8.00)	13.60 (6.00)	0.046
Age, years	47.00 (16.00)	54.50 (12.00)	$< 0.0001$
BMI, kg/m <sup>2</sup>	25.87 (4.02)	26.80 (4.75)	0.034
Smokers (%)	32	35	NS <sup>b</sup>
Hyperlipidemia (%)	30	29	NS <sup>c</sup>
Hypertension (%)	31	42	NS <sup>c</sup>
Type 2 diabetes (%)	22	33	NS <sup>c</sup>
CRP, $\mu$ g/l	2000 (1500)	2600 (1700)	0.013
Total testosterone, nmol/l	16.8 (7.3)	16.5 (8.1)	NS
Fasting glucose, mmol/l	5.27 (0.77)	5.61 (1.83)	0.0008
HDL-c, mmol/l	1.20 (0.28)	1.28 (0.35)	NS
LDL-c, mmol/l	3.20 (0.79)	3.33 (1.00)	NS
Cavernous a. PSVs, cm/s	37.00 (14.00)	43.00 (19.00)	NS

Abbreviations: BMI, body mass index; Cavernous a. PSV, cavernous arteries peak systolic velocity; CC-IMT, common carotid arteries intima-media layer; CRP, c-reactive protein; ED, erectile dysfunction; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SHIM, Sexual Health Inventory for Men.

Values are expressed as median (interquartile range).

<sup>a</sup>Wilcoxon rank-sum test.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>Two-sample test of proportions.

95%: 1.38–8.15; SHIM score  $\leq 9$ : OR 2.60, CL 95%: 1.01–6.70), while all other co-variables did not affect the OC dimension score ( $P > 0.05$ ). Psychological features other than OC were not significantly associated to the list of co-variables.

## Discussion

Even though psychological factors related to sexual dysfunctions constitute a quite complex and multi-dimensional construct, we explored this issue by using a screening instrument as a self-administered questionnaire (SCL-90-R). This study shows that approximately one out of three patients attending a government-subsidized Andrology outpatient clinic because of primary ED reported a psychological disturbance. A higher prevalence of psychological features, including interpersonal sensitivity, somatization, phobic anxiety and depression, was present in ED associated to preclinical atherosclerosis. Among the different psychological features, OC dimension resulted significantly associated to a vascular damage and to a severe ED, while other variables including aging, elevated BMI and a broad range of other VRFs did not affect the OC dimension score. Therefore OC features could independently predict ED in men with preclinical atherosclerosis. ED patients reporting a high score for OC features appear anxious, tense and agitated in their distress.<sup>26</sup> Performance anxiety, loss of self-esteem and a reduced quality of life are prevalent in ED,<sup>27</sup> and underscore a high level of mental stress associated with sexual dysfunction. OC features, and consequent low ability to cope with potentially stressful circumstances,<sup>28</sup> might be surmised as a potential risk for ED, mostly in men with preclinical atherosclerosis, which show a more severely deranged erectile function.<sup>18</sup>

Mental stress has been linked to an increased autonomic sympathetic activation<sup>29</sup> that results in an enhanced platelet activation and aggregability and increased circulating level of fibrinogen and thromboxane A2 with consequent risk for arterial thrombosis.<sup>12,30</sup> Indeed, a possible causal relationship between psychological distress and increased risk for acute vascular events has been extensively documented. Personality traits and psychiatric disorders are significantly associated to cardiovascular diseases. Phobic anxiety and panic disorders are associated with higher self-reported prevalence of hypertension, high cholesterol and diabetes<sup>11</sup> as well as with heart attack and stroke.<sup>31</sup> A prospective 2-year follow-up in a large population of middle-aged, elderly men demonstrated a causal association between phobic anxiety and fatal CHD.<sup>11</sup> A positive independent association has also been demonstrated for depressive symptoms and development of CHD<sup>12</sup> or fatal stroke,<sup>13</sup> as well as for self-reported

clinical depression and subsequent CHD.<sup>32</sup> Chronic mental stress may link ED and vascular damage by activating a reciprocal exacerbating mechanism. Psychological symptoms, such as OC dimension, may function as favoring or precipitating factors for ED  $\leftrightarrow$  vascular disease constellation. Alternatively ED symptom, which was more severe in men with preclinical atherosclerosis,<sup>18</sup> may favor OC features with a more pronounced and 'repeated' check auto-scrutiny to the 'affected organ'. Moreover, the analysis restricted to men attending an ED clinic might also favor a higher prevalence of patients with OC features, which include perfectionism, rigidity and problem-delegating traits. This bias should be recognized. It must also be acknowledged that our SCL-90-R evaluation could be considered a psychopathological screening, and by no means it can substitute a proper research criteria-based diagnostic evaluation such as Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.<sup>33</sup> In this light, our findings should be considered as preliminary, and more accurate diagnostic workup should be conducted in further studies.

ED in healthy men represents an independent risk factor for subsequent cardiovascular events.<sup>14</sup> A defect in the peripheral vascular generating nitric oxide-3'-5'-cyclic guanosine monophosphate system in the smooth muscle is suggested to generate ED and a vascular damage; the latter being accelerated by concomitant VRFs.<sup>15</sup> The psychological distress activated by ED in men with non-favorable personality traits may increase the risk for CHD in case of associated VRFs, based on the association between psychological distress and increased risk for acute vascular events in middle-aged, elderly men.<sup>11–13,31,32</sup> ED treatment might be therefore viewed as aimed to reduce psychological risk factors for future cardiovascular events. The introduction of validated multidimensional self-report questionnaires to identify psychological distress may help in identifying men deserving a more vigorous and prompt ED treatment. Based on the present study, this seems particularly relevant for men at above average risk for vascular events who show evidence for preclinical atherosclerosis. Prospective studies should elucidate the possible relationship of psychological features and VRFs in generating ED and cardiovascular disease.

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