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REVIEW

Is erectile dysfunction a reliable indicator of general health status in men?

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ABBREVIATIONS

ED, erectile dysfunction;
EF, erectile function;
DM, diabetes mellitus;
CVD, cardiovascular disease;
MeS, metabolic syndrome;

Abstract ***Introduction:*** Erectile dysfunction (ED) is a common risk factor in men and its incidence increases with age. Ageing and older men frequently have comorbidities such as cardiovascular diseases (CVD), diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease and dyslipidaemia; likewise, they concurrently refer to a clinician for impairments in sexual function, mostly for ED. The association of ED and other organic, multi-organic or even systemic diseases is widely described, with a specific emphasis on the fact that they often share common pathophysiological factors and mechanisms. Thus we reviewed previous reports assessing the role of ED as a sentinel marker of overall men's health.

Discussion: ED is considered an important sentinel marker for CVD. Numerous studies have highlighted the predictive role of ED for subsequent CV events in patients with a silent history of coronary artery disease. Indeed, ED might be considered as a clinical manifestation of a generalised vascular disease, and it should provoke clinicians to check for CVDs in those patients complaining of impaired erectile function. This concept appears to be even more important for men with DM, where ED has already been shown to have a significant predictive ability for major vascular complications. Moreover, data from large population-based studies showed that ED is a significant predictor of all-cause mortality, in addition to CV

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COPD, chronic obstructive pulmonary disease;
QoL, quality of life;
IIEF, International Index of Erectile Function;
CCI, Charlson Comorbidity Index;
CAD, coronary artery disease;
MMAS, Massachusetts Male Aging Study;
CHD, coronary heart disease;
HF, heart failure

outcomes. The severity of erectile function is assessed with the International Index of Erectile Function-Erectile Function domain score, and this has emerged as a proxy for men's general health status, as assessed with the Charlson Comorbidity Index score.

Conclusions: Patients complaining of ED should be evaluated with a comprehensive medical and sexual history, and a thorough physical examination, regardless of their age, considering ED as an opportunity to screen for the presence of health-threatening concomitant comorbidities.

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Introduction

Sexual health is a crucial aspect of overall health [1,2]. Data suggest that sexual health declines as a function of age in men, while concomitant comorbidities increase throughout the life span [3]. Specifically this is the case for erectile function (EF), a complex multisystemic process that has been extensively studied over the last decades. In this context, erectile dysfunction (ED) is defined as the recurrent or consistent inability to obtain and/or to maintain a penile erection sufficient for satisfactory sexual performance [4,5].

Several studies reported that the prevalence of ED is 2–9% in the decades from 40 to 49 years, and 20–40% for men aged < 69 years, while reaching a higher prevalence in men in their 70 s and 80 s [6]. The ageing process is accompanied by a progressively increasing organic impairment; therefore, the more that the global population ages, the more it becomes affected by several comorbidities [3]. Several studies highlighted the significant association between ED and other conditions such as diabetes mellitus (DM), cardiovascular disease (CVD), hypertension, dyslipidaemia, obesity, metabolic syndrome (MeS), depression, chronic obstructive pulmonary disease (COPD), and LUTS [7–10]. Furthermore, ED seems to share common aspects of its pathophysiological mechanisms with those involved in several of these potential comorbid conditions [11], thus suggesting that ED should be considered not only as a direct consequence of a concomitant disease, but that it could also have a leading role as a primary manifestation of the underlying disorder. Indeed, ED has emerged as an important sentinel marker of men's overall health, assuming major relevance in the cardiovascular field [12–16].

Thus if a patient complains of severe ED, it is possible to infer that he might also have underlying comorbid conditions, and consequently that such men might need a more comprehensive medical assessment, irrespective of age [17–19]. Conversely, it will be possible to infer that patients with a significant burden of comorbid diseases can also have a severe form of ED [20], deserving appropriate attention in terms of sexual health and quality of life (QoL). In this context, we previously [21] showed that the severity of ED, as objectively interpreted with the EF domain of the International Index of Erectile Function (IIEF), accounts for a higher Charlson Comorbidity Index (CCI), which can be considered a reliable proxy of a lower general health status, regardless of the cause of ED.

The aim of this review was to systematically assess previous reports of the association between ED and major comorbid conditions such as CVD, DM, and other organic, multi-organic and systemic conditions, while discussing the potential role of ED as a proxy of men's general health.

ED, CVD and DM

Sexual dysfunction can have a major effect on QoL, and on psychosocial and emotional well-being. For these and many other reasons, ED and all other male sexual problems represent common medical conditions that need to be managed by a multidisciplinary approach [2]. Starting from these assumptions, ED and the other sexual dysfunctions become even more important considering all other reported data suggesting that the incidence of different morbidities increases among European men as a function of age, and that simultaneously ageing and older men are affected by ED and severe orgasmic impairment, both closely associated with concomitant comorbidities [3]. In this context, ED, which for a long time was considered as a secondary complication of CVD [22–24], or regarded as a late consequence of generalised arterial disease [25], has progressively emerged as an important sentinel marker of men's

overall health, above all considering the field of CVD. A study in the USA analysing 9457 men with no history of CVD, followed from 1994 to 2003, showed a 45% greater risk of CV events in men with ED than in those without ED ($P < 0.001$), a risk equivalent to that for men currently smoking [26]. Likewise, in 2003 a study by Montorsi et al. [27], the aim of which was to assess the prevalence of ED, time of onset, and the association with risk factors in patients with acute chest pain and angiographically documented coronary artery disease (CAD), showed that a significant proportion of those patients also complained of ED, and the condition could become evident even before symptoms of angina in almost 70% of cases (mean interval 38.8 months). Moreover, all patients with type I DM and concomitant ED actually developed sexual dysfunction before the onset of CAD. Vlachopoulos et al. [16] comprehensively analysed 50 asymptomatic men with non-psychogenic and non-hormonally caused ED, using an exercise treadmill test, stress echocardiography and eventually coronary arteriography in all men. They showed that almost 19% of the entire cohort with ED of vascular origin had angiographically documented silent CAD; therefore, on the one hand, they concluded that ED might act as a marker for silent CAD, which certainly deserves to be accurately and routinely excluded, and on the other hand, men with CAD frequently had ED that can be treated safely [28]. Lastly, Chew et al. [29] underlined that the predictive ability of ED for subsequent atherosclerotic CV events is even more striking when ED emerges at a younger age. This concept is reinforced by the study of Riedner et al. [18], who showed that men aged < 60 years and complaining of ED also had a higher risk of having chronic CAD, and more severe disease diagnosed by coronary angiography. Hence, ED should be considered as a clinical manifestation of a generalised vascular disease also affecting the penile arteries.

One reason that might partly explain the association between ED and CVD is that both these conditions share common risk factors, including cigarette smoking, obesity, dyslipidaemia, hypertension, DM, MeS, and sedentary behaviour [30–40].

Likewise, it has been also shown that lifestyle modifications and a rational modification of the pharmacotherapy for CVDs might eventually be effective for improving sexual functioning in men with ED [18,38,41–44]. Specifically, the effects of these common risk factors on endothelial function might be a central mechanism for both diseases. Indeed, there is increasing evidence that endothelial dysfunction is a common aetiological factor for ED and CV events; indeed, even men presenting with ED, although with no established atherosclerotic disease, had an overall worsened endothelial function [45,46].

Several studies have investigated the link between ED and CVD among patients with DM [37,40,47–49]. DM is a well-known risk factor for ED and its association with ED is widely reported. Men with DM have three to four times the risk of developing ED than non-diabetic men; moreover, ED can emerge as the presenting symptom of DM in some men [50]. According to the Massachusetts Male Aging Study (MMAS), men with DM have a 28% prevalence of ED, compared with 9.6% in the general population [47]. Similarly, a multicentre study of 1312 diabetic men showed that the prevalence of ED in this specific group was 64.4%; more specifically, a duration of DM of > 10 years, together with a patient's age > 60 years, emerged as the major risk factors for ED [51]. Sairam et al. [52] investigated the prevalence of undiagnosed DM in a cohort of 122 men with ED and referred to an andrology outpatient clinic in the UK. Among this relatively small group of diabetic men they found a prevalence of 4.7% of undiagnosed DM and another 3.7% with either impaired glucose tolerance or impaired fasting glycaemia. Historically, a similar study showed a 12.1% prevalence of a still-undiagnosed DM in men with impaired EF [53]. These findings seem to underline the importance of ED as a symptom of other comorbid conditions, such as DM. Overall, the authors of these reports, and the present authors, suggest the need to testing fasting blood glucose as a screening tool in patients complaining of impaired EF, thus preventing and avoiding the long-term complications of DM. This will ultimately prove to be even more important for patients with type 1 DM [54].

Patients affected by DM are also at a higher risk of CVD than are the general population, and CAD represents the main cause of death among diabetic patients [55–57]. Moreover, CAD is often asymptomatic in diabetic patients [50,58,59], thus potentially leading to a more or less severe delay in its diagnosis, as well as in the subsequent appropriate treatment, It is often detected in an advanced state, when both starting an effective treatment and modifying the natural history of the disease becomes more difficult [60–62]. Because of this, there is an urgent need for a new marker for silent CAD in diabetic men, with the specific aim of improving the detection rate. In this context, ED has a potential predictive role for CV events, especially in diabetics [12–14,27,63]. Therefore, ED could be considered as an important tool in making an earlier diagnosis of CVD in this subset of patients [27,50]. Ma et al. [64] examined the potential risk factors for coronary heart disease (CHD) events in 2306 Chinese men with type 2 DM with no clinically overt CVD; ED was an independent predictor of CHD events after adjusting for other confounding factors, such as age and duration of DM per se. Similarly, Batty et al. [15] reported a study examining the relationship between erectile problems in men with type 2 DM and death from CVD. The authors confirmed previous findings that ED was associated with a

range of CVD, CHD and cerebrovascular events. García-Malpartida et al. [65] evaluated the rate of ED among men with type 2 DM and no macroangiopathy, also trying to assess the association between ED and CV risk factors, chronic complications of DM, silent myocardial ischaemia and peripheral arterial disease. The authors showed that ED is highly prevalent in DM, and is clearly associated with the presence of silent myocardial ischaemia, a higher systolic blood pressure and chronic microvascular diabetic complications [65].

Overall, taking all these data, ED should be regarded as a clinical manifestation of a systemic vascular disorder involving both the penile and coronary circulation in the general population and, even more significantly, in diabetic men, for whom having ED might give about a 1.4-fold higher risk of CAD than in men with no ED [50].

Heart failure (HF) is a complex clinical syndrome which can result from any structural or functional cardiac disorder that eventually impairs the ability of the ventricle to fill with, or to eject, blood. The incidence and prevalence of HF are constantly increasing in western countries, because of the reduction in fatal myocardial infarction and a longer average life span [66]. Total absence of sexual activity is reported by 30% of patients with HF. Moreover, the HF-induced reduction in exercise tolerance, side-effects of medications for HF and the coexistence of shared risk factors between HF and sexual dysfunction might further aggravate the sexual health of patients with HF [67]. Shared risk factors, common pathogenic traits and epidemiological association represent some of the links between HF and ED [67]. Indeed, ED has been recognised as an earlier predictor of CV events and cardiovascular death; moreover, HF itself can cause and/or worsen ED because of its particular features and comorbidities, ranging from impaired exercise tolerance to psychogenic factors and neurohumoral, metabolic and vascular modification. Furthermore, some cardiovascular drugs can contribute to impaired EF [67].

ED and men's overall health. The case for comorbidities other than CVD

Besides the important link between ED and CVD, a significant but incompletely known correlation between ED and other comorbid conditions has been outlined, with an impressive direct effect on men's overall health [12,31,68–74]. In this context, several epidemiological surveys have highlighted the association between ED and conditions like respiratory disorders, connective tissue disorders, kidney and liver impairment and neurological diseases. In other words, ED is usually associated with systemic disorders. For instance, a large survey conducted on >2000 patients with ED in Taiwan showed that ED is associated with a higher prevalence of many non-cardiovascular comorbidities [71]. Chung et al. [71] conducted a cross-sectional analysis between a group of patients with a diagnosis of ED and a group of >11,000 age-matched men who had never complained of ED, with the specific aim of investigating the prevalence and the risk of having one or more of 22 selected comorbidities for patients with and without ED. The authors found a significantly higher risk of gastrointestinal diseases, like peptic ulcer and liver diseases, in men with ED than in men without ED. An impaired release of nitric oxide was suggested as the pathophysiological link between ED and the different gastrointestinal disorders [75,76], while the mechanism behind ED in patients with liver disease remains unclear. Toda et al. [77] confirmed the association of ED with liver cirrhosis and chronic hepatitis, with a direct correlation of the severity of ED with liver impairment, as graded using the Child-Pugh classification, and with serum albumin level. Moreover, patients with ED had a higher prevalence of COPD [71], thus confirming several studies reporting an increased prevalence of ED in patients with COPD [72,73]. In a prospective study on 60 men with COPD, ≈75% of the patients were found to have ED [78], with half of them being free of the other comorbidities usually associated with ED. Sustained systemic inflammation is considered to be the pathophysiological link between ED and COPD [11], together with other predisposing factors like compromised pulmonary function, hypoxia, smoking and physical restriction [79–82]. A nationwide population survey conducted in Taiwan also showed that asthma, as a chronic airway inflammatory disorder, seemed to be associated with ED [69]. The authors explored the relationship between these conditions in patients aged 18–55 years who were newly diagnosed with asthma; in parallel, they selected an age-, gender- and comorbidities-matched control group of patients without asthma. Subsequently, the two groups were followed to evaluate the rate of the development of ED over time. Interestingly, the authors found a significantly higher incidence of developing ED in the asthmatic group than in the control group [69]. Systemic inflammation would seem to play a major role in the link between these conditions, as a potential reason for endothelial dysfunction [11], which is again a crucial factor in the pathogenesis of ED [45,75,76,83,84]. Indeed, data suggest that cytokines involved in asthma, such as leukotrienes, bradykinin, reactive oxygen species and TNF-α, might have affected the overall vascular function in patients with ED [84]. In a preliminary study, Vlachopoulos et al. [85] showed that sexual performance (as assessed using the IIEF-5 score) was inversely correlated with the circulating levels of endothelial prothrombotic and inflammatory variables, e.g., fibrinogen, von Willebrand factor, interleukin-6 and interleukin-1β. At the same time, the human corpus cavernosum per se might contribute to exacerbate a systemic inflammation, as an angiotensin II-producing

paracrine system [86]; this system could be overactive in men with organic ED [87], thus triggering vascular inflammation by regulating the release of inflammatory mediators and by inducing oxidative stress [88]. The concept of systemic inflammation has been identified as the basis of the pathogenetic mechanism accounting for the association of ED, CVD and MeS, the last defined as the coexistence of central obesity, hypertension, dyslipidaemia and insulin resistance [70]. Several epidemiological surveys support the association between ED and MeS [10,73,88–90]. In a study conducted on 2371 volunteers, MeS was independently associated with a decreased IIEF-5 score, while the waist-to-hip ratio was associated with a higher proportion of moderate to severe ED [73]. Conversely, Kupelian et al. [91] conducted a survey on a population of men from the MMAS who developed MeS during an observation period of ≈5 years, and they found that ED was predictive of the subsequent development of MeS in patients with a normal body mass index at baseline, thus stressing the value of ED as a warning sign in men otherwise considered at low risk of CVD, and who should be motivated to adopt a long-term healthy lifestyle. Therefore, the onset of ED might indicate the need for a more regular assessment of blood pressure and lipid profile, and for any improvement in lifestyle, such as regular physical exercise and a healthier diet. In this context, Shabsigh et al. [92] attempted to develop a calculator to define which men with ED had a higher chance of developing other morbidities such as DM, hypertension, hyperlipidaemia or even angina. Data were collected from a multinational population-based study (the MALES study), including patients evaluated for ED and general health conditions. The authors analysed which variables were significantly correlated with the risk of any comorbidity of interest, and they devised a comorbidity risk calculator which included self-reporting the severity of ED as one of the predictive factors, thus stressing again the role of ED as a key factor in calculating the probability of major risks to men's health [92]. In a large prospective population-based study, including data from 95,000 patients assessed with a general health questionnaire, to investigate the relationship of severity of ED as a marker of risks for all cause-mortality, Banks et al. [93] showed twice the risk of death from all causes in those men with severe ED than in men with no ED, regardless of the past history of CVD. This association showed no significant variation after accounting for age, cigarette smoking, alcohol consumption, physical activity, body mass index, DM, hypertension, and/or treatment for hypercholesterolaemia [93]. Moreover, using data from the MMAS dataset, Araujo et al. [94] examined the association of ED with all-cause mortality and cause-specific mortality. The study included 1655 men with a mean follow-up of 15 years, and the results showed that men with ED had worse overall health, with a 26% higher risk of all-cause mortality, and a 43% higher risk of death due to CVD, than had men without ED [94]. These findings were also confirmed by a meta-analysis, which included data from 92,757 subjects and considered all the longitudinal studies evaluating the ability of ED to predict the risk of clinical events [95]; Vlachopoulos et al. investigate the risk for all-cause mortality showing that this was significantly higher in individuals who had ED as compared with the risk in individuals without ED, with a relative risk of 1.25 (95% CI, 1.12–1.39). Therefore, Vlachopoulos et al. [95] showed that ED is a significant predictor of all-cause mortality, in addition to cardiovascular outcomes. These authors stated that this predictive ability could be the expression of a pathogenetic substrate, including ageing, systemic inflammation and oxidative stress.

They also suggested a role for depression as a factor that worsened the outcome of comorbid physical conditions. Indeed, depression is a condition strongly associated with ED [9,31,68]; for instance, in the MMAS, the age-adjusted probability of moderate or severe ED in patients with the maximum degree of depression was nearly 90% [31]. However, there is a clear bi-directional relationship between these two conditions; in this context, ED can be considered as a symptom of depression, but it might be also a consequence of the medications used to treat depression. Likewise, sometimes the social consequences of ED can eventually lead to depression. Moreover, they can both be considered as manifestations of underlying factors such as endothelial dysfunction (which has been linked to the so-called vascular depression [96]) or of lower plasma testosterone levels (which might affect erectile functioning and have been associated with depression in older men [97]).

All of these findings suggest that ED could be one of the primary manifestations of different comorbid conditions, and they also suggest a role for ED as a sentinel marker of men's overall health. In this context, we conducted a study on 140 patients with new-onset ED who were assessed with a thorough medical and sexual history, including data on health-significant comorbidities as scored with the CCI [21], which is considered a reliable indicator of disease burden and a strong estimator of overall mortality [46]. We sought to assess whether EF, defined by the IIEF-EF domain score, was associated with health-significant comorbidities. Our findings showed that the CCI score worsened with increasing severity of ED, as depicted by lower IIEF-EF scores. In particular, both linear and logistic regression analyses showed that the severity of ED was an independent predictor of higher CCI scores, thus supporting the idea that ED could be linked to a lower level of general health, regardless of patient age [21]. More interestingly, the IIEF-EF emerged as potential proxy of overall male health status. However, the study was limited by the few patients included, which prevented an assessment of the

predictive ability of the severity of ED in a subcategory of patients free from CVD. Despite this, the clinical implications of these findings are the importance of taking a comprehensive medical and sexual history, and performing a comprehensive physical examination in all men with ED, regardless of their age, thus considering ED as an opportunity to screen for the presence of concomitant comorbidities [13,18,98–101].

Conclusions

ED is strongly associated with different comorbid conditions, including CVD, DM, MeS and COPD. Men presenting with ED have a greater risk of CVD, CHD, stroke, overall atherosclerotic and CV events. For these and several other reasons, clinicians should be aware of the importance of screening patients with ED for CVD, and vice versa; in this way, it might be possible to make an earlier diagnosis of ED in patients with CVD, that could consequently be treated properly, also improving their overall QoL and their psychosocial well-being. Likewise, that might lead to an earlier diagnosis of CV problems, thus allowing clinicians to start an appropriate therapy, eventually preventing serious clinical events as a consequence of CVD. This is even more important for DM; indeed, it is well known that in diabetics there is a high incidence of concomitant ED, and that they also have a higher risk of CVD than the general population. Moreover, CAD represents the main cause of death in diabetic patients, and unfortunately can often remain asymptomatic. Taking these observations together, ED is a sentinel marker for CVD in men with DM, and it becomes clear how an impaired EF in diabetic patients should be considered as a warning sign for the development of major vascular diabetic complications, prompting clinicians to impose a stricter control of the disease.

Moreover, patients with ED have a higher risk of all-cause death than has the general population, as a consequence of a common pathophysiological mechanism including ageing, systemic inflammation, and oxidative stress, with evidence suggesting a role for ED as a sentinel marker for comorbidities other than CVD. In this context, ED can be considered as a proxy for men's overall health status, supporting the idea that ED might ultimately represent an opportunity to screen for the presence of concomitant health-related disorders. However, additional studies in larger population-based cohorts are needed to characterise the potential role of the severity of ED as a harbinger of life-threatening disorders, at least in some men.

Conflict of interest

There is no conflict of interest.

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