



Erectile dysfunction in young patients is a proxy of overall men's health status

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Purpose of review

This article summarizes current findings supporting the role of erectile dysfunction as a proxy of general health status, with a focus on the young population.

Recent findings

Erectile dysfunction has been historically associated to increased cardiovascular risk and mortality. Several studies supported the role of erectile dysfunction as a predictive factor of subsequent cardiovascular events, acquiring significant importance even in young men. Similarly, erectile dysfunction emerged as a potential marker for metabolic alterations including diabetes mellitus and metabolic syndrome, eventually presenting as the initial manifestation of a dysmetabolic condition in young patients. Moreover, current epidemiologic data demonstrated a significant association of erectile dysfunction with several conditions including vascular, respiratory, gastrointestinal disorders, and endocrine with chronic-sustained inflammation representing the common pathophysiological link between erectile dysfunction and comorbidities. Interestingly, longitudinal studies demonstrated a higher risk of overall mortality in patients complaining of erectile dysfunction, even irrespective of cardiovascular risk.

Summary

Erectile dysfunction does not represent an uncommon condition among young men. Considering the amount of data demonstrating a strong correlation between several life-risky comorbidities and erectile dysfunction, a careful and comprehensive general health assessment of patients complaining of erectile dysfunction should be carried out, regardless of patient's age. The identification of erectile dysfunction as an early sign of a major comorbidity would allow the implementation of therapeutic measures aimed at improving the overall health status and life expectancy across the entire aging process.

Keywords

erectile dysfunction, overall health status, young men

INTRODUCTION

Sexual health is considered a cornerstone aspect of overall health [1]; indeed, in the last two decades erectile dysfunction has gained considerable importance in the field of general men's health status [2,3,4]. Several reports highlighted the significant association between erectile dysfunction and other conditions such as diabetes mellitus, cardiovascular disease (CVD), hypertension, dyslipidaemia, obesity, metabolic syndrome (MetS), depression, chronic obstructive pulmonary disease, and lower urinary tract symptoms [5–8]. In this context, numerous recent evidences allowed us to reconceptualize erectile dysfunction not only as a condition sharing several pathophysiological aspects with other comorbidities but it could also be considered as a primary manifestation of an underlying disorder, thus assuming the role of a sentinel marker of overall men's health [2].

It seems clear that the possibility to early detect potential life-risky morbidities such as CVDs, with a thorough physical and general health examination at the time of erectile dysfunction presentation, eventually acquires even more significant importance at younger age. The prevalence rate of erectile dysfunction has been historically demonstrated to increase throughout the aging period and especially

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KEY POINTS

- Erectile dysfunction is not an uncommon condition among young men below the age of 40 years.
- A strong correlation between CVD, diabetes mellitus, MetS, and erectile dysfunction has been widely reported, with erectile dysfunction being a sentinel marker for all these conditions, primarily at younger ages.
- Erectile dysfunction emerged as a proxy of overall health and it has been associated with a higher risk of overall mortality.
- A thorough medical assessment of young patients complaining of erectile dysfunction is of paramount importance for achieving an early identification of life-risky comorbidities.

after 40 years of age [9]; however, an increasing amount of data show that erectile function impairment in men below 40 years of age is far from being considered uncommon [10–12].

Aims of this review are to summarize the available evidences supporting the concept of erectile dysfunction as a proxy of overall health status, focusing on the young population, and analyse the link between erectile dysfunction and major comorbidities like CVDs, diabetes mellitus, MetS, and other conditions.

ERECTILE DYSFUNCTION AS A PROXY OF CARDIOVASCULAR DISEASES IN YOUNG MEN

The potential role of erectile dysfunction as a sentinel marker of coexisting and undetected diseases has been historically mainly investigated in the field of CVDs [5,6]. Montorsi *et al.* [5] clearly showed in a cohort of patients with angiographically documented coronary artery disease (CAD) that 67% of patients reported erectile dysfunction prior to CAD symptoms. Similarly, a further cornerstone study based on a subanalysis conducted within the placebo group of the Prostate Cancer Prevention Trial, incident or prevalent erectile dysfunction was significantly associated to a subsequent cardiovascular event throughout the follow-up with a range of risk similar to current smoking or family history for myocardial infarction [6]. A number of prospective studies confirmed the association of erectile dysfunction with CVDs and raised the concept of considering erectile dysfunction as a potential sentinel marker helping in an early identification of CAD [4,6,13]. In this context, Montorsi

et al. [14] showed that in 93% of the patients with established CAD, erectile dysfunction occurred on average 24 months before CVD diagnosis. However, the vast majority of these studies were conducted in a population of men with an age range of 40–80 years old [15]. Interestingly, Ponholzer *et al.* [16] assessed the rate of cardiovascular events occurred during a 6.5 years follow-up in a cohort of 2506 men of which 67% were 20–50 years old, all assessed with the International Index of Erectile Function-5 (IIEF-5) at baseline. The authors failed to show an association between erectile dysfunction and cardiovascular events ascribing their findings to the fact that most of the patients below 50 years of age included in their cohort had a short length of follow-up at the assessment date [16]. Conversely, in a retrospective study conducted on a cohort of 1660 men with erectile dysfunction and without previously reported atherosclerotic CVDs, the incidence of subsequent cardiovascular events was significantly higher in the erectile dysfunction group as compared with a general male population [17]; of even higher clinical significance, the younger the patient at the first erectile dysfunction manifestations the higher the hazard ratio for subsequent cardiovascular events, with a seven-fold increased risk in the age group of men younger than 40 years [17]. The authors underlined that such a time-to-event interval of several years between the manifestation of erectile dysfunction and a subsequent atherosclerotic cardiovascular event could be of significant advantage in terms of cardiovascular risk prevention [17]. These data were further confirmed in a meta-analysis of 14 longitudinal studies including 92 757 patients, which showed a higher relative risk of cardiovascular events in younger patients with erectile dysfunction [18]. All these findings, supported the well known hypothesis of erectile dysfunction as a manifestation of a generalized vascular endothelial disease, that used to appear earlier in the penile district given the considerable smaller size of penile arteries leading to a faster achievement of a clinically significant reduction in blood flow than in other vascular districts [5].

In this context, despite the fact psychogenic erectile dysfunction is usually considered the most prevalent form of erectile function impairment in young men, rates of vasculogenic erectile dysfunction have been reported to range from 32 to 72% of erectile dysfunction patients below the age of 40 [19]. Yao *et al.* [20], for instance, investigated the possible underlying pathogenesis of erectile dysfunction in 122 men below the age of 40 years old; to this regard, the authors compared the erectile dysfunction group with an age-matched control

group showing a higher level of systolic blood pressure, total cholesterol, high sensitivity C-reactive protein, greater carotid intima-media thickness, and a higher Framingham Risk Score (FRS) within the erectile dysfunction group, thus suggesting that endothelial dysfunction *per se* and low-grade inflammation could be considered the underlying pathogenesis of erectile dysfunction in young patients already harbouring a subclinical CVD [20].

Moreover, young adults may experience non-typical erectile dysfunction problems, including honeymoon erectile dysfunction, teenager erectile dysfunction, mild erectile dysfunction, unrecognized erectile dysfunction, and weaker masturbatory erection (WME), all of them usually ascribed by physicians to psychogenic factors [21]. However, Huang *et al.* [21] recently investigated the prevalence of common cardiovascular risk factors in a young population of men aged 18–40 years reporting WME, and they showed that compared with a nonerectile dysfunction group, WME individuals had higher prevalence of cardiovascular risk factors such as endothelial dysfunction and insulin resistance, thus suggesting that also WME may be a sign of early cardiovascular risk in young men.

For all these reasons, the current international clinical recommendations suggest a CVD screening in all erectile dysfunction patients, which should always start with the FRS calculation for an initial cardiovascular risk stratification [22]. In this context, Fang *et al.* [23] recently investigated the association between changes in erectile dysfunction status over time and cardiovascular risk as calculated with the FRS, in a population of 965 men free of CVDs. The authors showed that both transient and persistent erectile dysfunction were associated with a greater increase in FRS over time in men below 50 years of age, regardless of common CVD risk factors.

ERECTILE DYSFUNCTION AND DIABETES: A MARKER OF DISEASE AND A PROXY OF SEVERITY

Diabetes mellitus is a well known risk factor for erectile dysfunction and a significant correlation between both conditions has been widely reported [7,24,25]. Epidemiologic studies showed a three-fold increase of the probability of developing erectile dysfunction in patients with diabetes mellitus and reported a prevalence of erectile dysfunction of 35–90% among men with type 2 diabetes mellitus (T2DM) [7]. Behind the association of erectile dysfunction and diabetes mellitus, there are several pathophysiological factors, including peripheral

neuropathy, macro and microangiopathy, and endothelial dysfunction; this latter characterized by a decreasing of nitric oxide synthase activity, which results from a chronic insult of hyperglycaemia and oxidative stress; as a whole, this pathological condition eventually may lead to a significant reduction of the nitric oxide bioavailability, which in turn is crucial for penile erection [24].

In this context, it has been shown that erectile dysfunction could ultimately emerge as the presenting symptom of diabetes mellitus at least in some men. For instance, Sairam *et al.* [26] investigated the prevalence of undiagnosed diabetes mellitus in a cohort of 129 men with erectile dysfunction, showing a prevalence of 4.7% of undetected diabetes mellitus and another 3.7% of patients with either impaired fasting glycaemia or impaired glucose tolerance. Similarly, more recently 1417 men were screened for erectile dysfunction and assessed with a fasting glucose measurement; the findings showed a prevalence of 11.5% of undiagnosed diabetes mellitus in men with erectile dysfunction versus only 2.8% in men without erectile dysfunction [27]. Moreover, Maseroli *et al.* [25] recently looked at the prevalence of endocrine and metabolic disorders in a population of 3847 patients attending an outpatient clinic academic service for erectile dysfunction and they compared their findings with those of a general population-based sample derived from the European Male Aging Study. They reported a prevalence of impaired fasting glycaemia and T2DM of 44.5 and 20.1% versus 33.3 and 1% in the erectile dysfunction and control group, respectively. Of clinical relevance, the association between erectile dysfunction and T2DM reached statistical significance even after adjusting for patient's age [25]. Given these data, we may argue that erectile dysfunction could represent a manifestation of an initial metabolic disorder, which may result as one of the first symptoms even in younger men. Indeed, in a study conducted on a population of healthy men aged 26–45 years and aimed to assess factors predicting a subsequent diagnosis of T2DM occurring over the follow-up, the authors showed that higher fasting plasma glucose levels, although within the normoglycaemic range, constitute an independent risk factor for developing T2DM, especially in young men, with higher BMI and triglyceride levels apparently responsible for being a sort of premetabolic disorder, which could also be eventually associated with erectile function impairment [28]. In this context, Yao *et al.* [29] analysed the possible underlying pathogenesis of erectile dysfunction in men under the age of 40 years without well known cause; they showed that patients with

erectile dysfunction had significantly higher levels of the insulin resistance index (HOMA-IR), which has been previously associated with endothelial dysfunction, and thus suggesting that an early glycometabolic disorder may be an important mechanism behind organic erectile dysfunction in young patients [29]. Finally, the onset of erectile dysfunction within both an initial or an overt diabetes mellitus acquire even more importance as an independent cardiovascular risk factor in diabetic patients; indeed some large prospective trials previously confirmed that erectile dysfunction is a powerful predictor of CAD and cardiac mortality in patients with diabetes mellitus, which usually harbour occult myocardial perfusion abnormalities [15[¶]]. As a further evidence, Corona *et al.* [30] recently demonstrated that the application of an algorithm assessing metabolic risk and identifying prediabetes condition in a population of patients with erectile dysfunction, is able to predict long-term cardiovascular events, thus confirming the role of erectile dysfunction as a worsening factor of overall health in patients with diabetes mellitus and corroborating previous data showing higher levels of disease-specific health distress, poorer adaptation to their diabetes, and marked reductions in overall quality of life [31].

THE CASE FOR COMORBIDITIES OTHER THAN CARDIOVASCULAR DISEASE-ERECTILE DYSFUNCTION AS A MIRROR OF OVERALL HEALTH

Apart from CVDs and diabetes mellitus, several epidemiologic surveys have highlighted the association between erectile dysfunction and other comorbid conditions with an impressive direct effect over men's overall health [2,4,8,32]. In a large survey conducted on a cohort of 2213 men reporting erectile dysfunction and 11 065 matching controls without the disorder, Chung *et al.* [8] analysed prevalence and risk of 36 different comorbidities, showing an increased risk for multiple systemic comorbid conditions, thus including prostatitis, urinary incontinence, spondylitis, peripheral vascular disorder, ischaemic heart disease, psychoses, depression, diabetes, hepatitis, gastrointestinal diseases, hyperlipidaemia, and chronic pulmonary disease, apart from alcohol and drug abuse. The pathophysiological link between erectile dysfunction and comorbidities other than CVD has been in most cases ascribed to the presence of common predisposing factors such as smoking and physical restriction, together with the hypothesis of a sustained systemic inflammation state as an underlying potential reason for endothelial dysfunction [3].

Indeed, Vlachopoulos *et al.* [33] showed that sexual performance (as assessed using the IIEF-5 score) was inversely correlated with the circulating levels of endothelial prothrombotic and inflammatory factors such as fibrinogen, von Willebrand factor, IL-6, and IL-1 β . A chronic higher level of inflammatory mediators has also been considered the potential linkage between erectile dysfunction and respiratory disorders such as chronic obstructive pulmonary disease [3]. Interestingly, in a study involving a population of men aged 18–55 years with newly diagnosed asthma, compared with a matched control group without asthma, the occurrence of erectile dysfunction in a mean follow-up period of 4.6 years was significantly higher in the asthma group than in controls, with asthmatic patients experiencing a 1.9-fold increase in incident erectile dysfunction, which emerged to be independent of patient age [32]. The authors speculated that systemic inflammation has to be considered at the basis of this correlation, given previous data showing that cytokines involved in pathways supporting asthma condition eventually can affect vascular function in erectile dysfunction [34]. Similar factors have been thought to be responsible for the association between erectile dysfunction and MetS, which can be considered as a state of low-grade chronic inflammation resulting from a complex interplay between environmental and genetic factors that may be related to erectile dysfunction, and it is defined as a combination of impaired glucose tolerance, dyslipidaemia, hypertension, and central obesity [35]. The prevalence of MetS in patients with erectile dysfunction has been reported to range from 29 to 66% [36]. Moreover, data coming from the Massachusetts Male Aging Study showed that in a population-based cohort observed throughout almost 15 years, erectile dysfunction was predictive of MetS with an unadjusted relative risk of 1.35 even in men with normal weight at baseline [7]. In this context, in a recent study assessing the association of MetS and erectile dysfunction in a nationally representative US data sample, the authors showed that MetS was associated with more than 2.5-fold increased odds of self-reported erectile dysfunction and men aged 20–39 years showed the highest odds of erectile dysfunction, thus providing additional incentive for young men to improve lifestyle habits [37]. Furthermore, higher levels of insulin resistance have been associated with the presence of erectile dysfunction of unknown cause in patients below the age of 40 [29]. Insulin resistance is a metabolic alteration common in most patients with MetS and T2DM, and it has been considered responsible for a condition of endothelial dysfunction because of a lower synthesis and release of nitric oxide,

which is well known to hamper the vasodilator mechanism in different arterial districts, thus including the erectile tissue [29].

Moreover, MetS has been widely associated with testosterone deficiency; more specifically, the prevalence of testosterone deficiency has been shown to be three times higher in men with concomitant erectile dysfunction and MetS than in those without erectile dysfunction [38]. Association between MetS and testosterone deficiency may result in increased cardiovascular risk and low testosterone levels have been associated with higher risk of major adverse cardiac events and CAD mortality [39]. For these reasons, erectile dysfunction may result in a valuable opportunity to detect testosterone deficiency, and thus identifying patients at increased risk of MetS and cardiovascular risk.

In light of all these data, Salonia *et al.* [2] looked for a potential correlation between erectile dysfunction severity and general health status in a cohort of 140 patients with new-onset erectile dysfunction. They demonstrated a significant correlation between IIEF-Erectile Function domain (IIEF-EF) score and the Charlson Comorbidity Index score, thus providing novel evidence that erectile dysfunction severity, as scored with the IIEF-EF, may be linked with several comorbid conditions other than CVDs; interestingly, the correlation between erectile dysfunction severity and the burden of comorbidities was independent of patients' age and erectile dysfunction cause [2]. Finally, the role of erectile dysfunction as an indicator of general health status has been further strengthened by data showing a correlation between erectile dysfunction and all-cause mortality irrespective of cardiovascular-specific mortality [18]. Indeed, in a longitudinal population-based study, including data from 95 000 patients, Banks *et al.* [4] showed twice the risk of death from all causes in those men with severe erectile dysfunction than in men with no erectile dysfunction, regardless of the past history of CVD; of major clinical importance, this association appeared even stronger in younger men, without significant variation after accounting for cigarette smoking, alcohol consumption, physical activity, BMI, diabetes mellitus, hypertension, and/or concomitant treatment for hypercholesterolaemia.

CONCLUSION

Erectile dysfunction is commonly considered a sexual complaint showing increasing rates throughout the aging process; in contrast, the prevalence of reported erectile difficulties among young men is not invariably low, with epidemiologic studies

showing rates of erectile dysfunction ranging between 2% and nearly 40% in individuals younger than 40 years of age. Moreover, numerous data show comparable rates of severe erectile dysfunction between younger and older patients, thus highlighting the need not to underestimate this clinically meaningful condition even in the younger population. Indeed, despite the fact that psychogenic factors are mainly responsible for sexual difficulties in most of the young individuals, a considerable amount of young men could even suffer from pure organic erectile dysfunction. In this context, a huge amount of data support the theory of a sustained inflammatory state leading to a series of metabolic and vascular alterations, including endothelial dysfunction, which is responsible for erectile dysfunction *per se* and may represent the common link between erectile dysfunction and several life-threatening conditions. Men presenting with erectile dysfunction have a greater risk of CVD and overall atherosclerotic and cardiovascular events, whose pathologic process may start several years before their first appearance whereas it becomes evident with erectile dysfunction. This is even more important in diabetic patients for whom an impaired erectile function should be considered as a warning sign of a future development of major vascular complications; this should prompt clinicians to start with a close control of the disease. Furthermore, erectile dysfunction has been associated with a lower male general health status, with longitudinal studies showing a higher risk of overall mortality for men reporting erectile dysfunction, irrespective of age and concomitant cardiovascular risk.

Moving to the daily clinical practice, current findings underscore the need for taking a comprehensive medical and sexual history, along with a thorough physical examination in all men with erectile dysfunction; this appears to be even more clinically meaningful in young men, with the aim not only to treat a bothering condition in potentially more sexually active individuals but also to start and support lifestyle changes or even adopting specific treatments aimed at improving the overall health status, life expectancy, and psychosocial well-being.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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