The Aging Male

ISSN: 1368-5538 (Print) 1473-0790 (Online) Journal homepage: informahealthcare.com/journals/itam20

Erectile dysfunction, loss of libido and low sexual frequency increase the risk of cardiovascular disease in men with low testosterone

Chen-Hsun Ho, Chia-Chang Wu, Kuan-Chou Chen, Fu-Shan Jaw, Hong-Jeng Yu & Shih-Ping Liu

To cite this article: Chen-Hsun Ho, Chia-Chang Wu, Kuan-Chou Chen, Fu-Shan Jaw, Hong-Jeng Yu & Shih-Ping Liu (2016) Erectile dysfunction, loss of libido and low sexual frequency increase the risk of cardiovascular disease in men with low testosterone, The Aging Male, 19:2, 96-101, DOI: 10.3109/13685538.2015.1129400

To link to this article: https://doi.org/10.3109/13685538.2015.1129400

Published online: 11 Jan 2016.

The Aging Male

http://informahealthcare.com/tam
ISSN: 1368-5538 (print), 1473-0790 (electronic)

Aging Male, 2016; 19(2): 96–101
 DOI: 10.3109/13685538.2015.1129400

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Erectile dysfunction, loss of libido and low sexual frequency increase the risk of cardiovascular disease in men with low testosterone

Chen-Hsun Ho[1,2], Chia-Chang Wu[1,2], Kuan-Chou Chen[1,2], Fu-Shan Jaw[3], Hong-Jeng Yu[4], and Shih-Ping Liu[4]

[1]*Department of Urology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan,* [2]*Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan,* [3]*Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan, and* [4]*Department of Urology, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan*

Abstract

Introduction: Testosterone deficiency increases the cardiovascular disease (CVD) risk.
Aim: To evaluate the effect of erectile dysfunction (ED), sexual frequency and hypogonadal symptoms on CVD risk.
Methods: A total of 395 hypogonadal men aged 45–74 years were surveyed using the Androgen Deficiency in the Aging Male and the International Index of Erectile Function.
Main outcome measures: The 10-year CVD risk was measured with the Framingham Risk Score. Logistic regression was performed to obtain the odds ratios of sexual function and hypogonadal symptoms for a 10-year CVD risk $\geq$20% (high risk).
Results: The mean age was 56.1 ± 6.7 years. The mean 10-year CVD risk of the whole cohort was 18.1% ± 11.4%, while 131 subjects (33.2%) were classified as high risk. Logistic regression revealed that ED severity was associated with CVD risk [OR = 2.37 (CI 1.24–4.51) for mild-to-moderate ED, OR = 4.39 (1.78–8.43) for moderate ED and OR = 12.81 (4.65–26.11) for severe ED]. Compared to sexual frequency <1 per month, sexual frequency $\geq$4 decreased the risk of high CVD risk [OR = 0.35 (0.23–0.780)]. Loss of libido [OR = 2.95 (1.91–4.12)] and less strong erection [OR = 3.87 (CI 2.11–4.95)] increased the risk of high CVD risk. All remained significant after adjustment for age and testosterone.
Conclusions: ED, decreased sexual frequency and loss of libido predict a high 10-year CVD risk in hypogonadal men.

Keywords

Testosterone, erectile dysfunction, cardiovascular disease, hypogonadism, libido, Framingham Risk Score

History

Received 11 August 2015
Revised 9 November 2015
Accepted 4 December 2015
Published online 11 January 2016

Introduction

Testosterone deficiency (TD) is highly prevalent in men with obesity, type 2 diabetes and metabolic syndrome [1–5]. These metabolic disorders facilitate the development of arthrosclerosis through the mechanism of inflammation, endothelial dysfunction and increased intimal thickness. Moreover, TD itself also negatively impacts on vascular dynamics and the reactivity of blood vessels [6,7]. These negative impacts on cardiovascular health were supported by a substantial body of evidence, which revealed that TD increases the risk of cardiovascular disease (CVD) death and all-cause mortality [8–11]. From a therapeutic perspective, while it has been shown that testosterone replacement therapy prevents cardiovascular events in hypogonadal men [12–14], some recent studies have reported the opposite effect [15,16]. Before this controversy can be resolved, it is paramount for clinicians to evaluate the CVD risk and to recognize the associated risk factors in hypogonadal men [17].

Clinically, hypogonadal men may present with various symptoms, including those within the somatic, psychological and sexual domains [18,19]. It has been documented that sexual symptoms and in particular erectile dysfunction (ED), low libido and frequency of nocturnal erections are the most important symptoms associated with TD [20]. Moreover, sexual dysfunction is closely linked to some highly prevalent comorbidity of TD, such as obesity [4,5]. Moreover, a recent meta-analysis including all available placebo-controlled randomized controlled trials demonstrated that testosterone supplement improves all sexual symptoms in hypogonadal men [21]. All of the above evidence supports that sexual dysfunction is the core symptom of TD.

However, there is significant heterogeneity regarding the spectrum and the severity of symptoms in the hypogonadal population. According to the Boston Area Community Health (BACH) Survey, low libido and ED account for 28.1% and 27.7%, respectively, of the men with low testosterone, and

Address for correspondence: Hong-Jeng Yu, MD and Shih-Ping Liu, MD, Department of Urology, National Taiwan University Hospital and College of Medicine, No. 7, Chung-Shan South Road, Taipei 10001, Taiwan. Tel: +886 223123456x65251. Fax: +886 223219145. E-mail: yhj5251@ntu.edu.tw (H.-J. Yu); spliu@ntuh.gov.tw (S.-P. Liu)

only 42.8% present with at least two nonspecific symptoms [22]. These epidemiologic data indicate that a significant portion of TD is clinically asymptomatic and undiagnosed. As these asymptomatic men may be less likely to receive medical care or evaluation, their cardiovascular health has rarely been reported in the literature. Moreover, the role of these hypogonadal symptoms in determining CVD risk has not yet been clearly defined.

Aims

We conducted a study to investigate the effects of somatic, psychologic and sexual hypogonadal symptoms on CVD risk in a cohort of middle-aged and older men with low total testosterone. We aimed to clarify whether these aging symptoms predicted future CVD and if the asymptomatic hypogonadal men required medical attention.

Methods

Subjects

The study subjects were enrolled from a cohort of 1306 men who received sex hormone examination as part of their health examination at our institute in the year 2009. Those who were aged 45–74 years and had total testosterone <350 ng/dL constituted the study cohort. All subjects were interviewed by a physician, reporting their medical history and receiving a detailed physical examination. The protocol was approved by the institutional review board (201207058RIC).

Sex hormone and biochemical data

All subjects received blood sampling twice. The first blood sample, collected between 8 am and 10 am after overnight fasting, was used to measure the total testosterone, sex-hormone binding globulin (SHBG), and other biochemical concentrations. The second blood sample, collected two hours after a standard lunch, was used to measure the postprandial glucose. Total testosterone and SHBG were measured with a chemiluminescent microparticle immunoassay using the Architect Testosterone Reagent kit (Abbott Laboratories, Chicago, IL) and Architect SHBG Reagent kit (Abbott Laboratories), respectively. Free testosterone concentrations were calculated using the Vermeulen's formula [23].

Evaluation of low testosterone symptoms

All subjects were asked to complete two self-administered questionnaires to evaluate the associated aging symptoms and sexual function: the Androgen Deficiency in the Aging Male (ADAM) [24] and the International Index of Erectile Function (IIEF-5) questionnaires [25]. ED was defined as any total score value <21. ED severity was classified as follows: mild-to-moderate (12–21), moderate (8–11), and severe (5–7).

Evaluation of the risk of CVD

The CVD risk was determined using the Framingham Risk Score, which is a sex-specific algorithm used to estimate the 10-year risk of CVD, including coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease and heart failure [26]. A 10-year CVD risk was classified as low (<10%), intermediate (10–20%) and high (≥20%).

Main outcome measurements

Logistic regression was performed to the odds ratios of ED, sexual frequency, loss of libido and other hypogonadal symptoms for predicting a high CVD risk (10-year CVD risk ≥20%). Multivariate analyses were performed to adjust for confounders, including age, and total or free testosterone. Continuous data are presented as the mean ± standard deviation, and categorical data are presented as count and percentage (%). Two-tailed $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed on SPSS 17.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

A total of 395 men fulfilled the inclusion criteria and were enrolled in the current study. The characteristics of the whole cohort are shown in Table 1. The mean age was 56.1 ± 6.7 years. The mean total testosterone, free testosterone and SHBG were 278.3 ± 53.5 ng/dL, 6.2 ± 1.3 ng/dL and 23.3 ± 8.2 nmol/L, respectively. A total of 210 (53.2%), 61 (15.4%) and 169 (42.8%) had hypertension, diabetes mellitus and metabolic syndrome, respectively. The 10-year CVD risk was 18.1% ± 11.4%; 98 (24.8%) were low CVD risk, 166 (42.0%) were intermediate risk and 131 (33.2%) were high risk. The mean IIEF-5 score was 19.4 ± 4.9, and 86 (21.8%), 102 (25.8%), 55 (13.9%) and 44 (11.1%) were classified as no, mild to moderate, moderate and severe ED, respectively. A total of 108 (27.4%) had no sexual activity in the past 6 months. The mean sexual frequency was 2.9 ± 2.2 times per month: 237 (60.0%) had sex less than once per month, 93 (23.5%) had sex 1–3 times per month and 65 (16.5%) had sex four times or more per month. A total of 349 (88.4%) were positive for the ADAM questionnaire.

Logistic regression analysis revealed that ED predicts a high 10-year CVD risk [OR = 2.37 (CI 1.24–4.51) for mild-to-moderate ED, OR = 4.39 (CI 1.78–8.43) for moderate ED and OR = 12.81 (CI 4.65–26.11) for severe ED] (Table 2). The association of moderate and severe ED with a high CVD risk persisted after adjustment for age and total or free testosterone. There was a positive trend between the ED severity and the risk of high 10-year CVD risk in all multivariate analyses.

Compared to sexual frequency of <1 per month, higher sexual frequency (≥4 per month) decreased the risk of high 10-year CVD risk [OR = 0.35 (CI 0.23–0.780)] (Table 2). The association persisted after adjustment for age and total or free testosterone. There was a trend demonstrating increased sexual frequency as a protective factor for high CVD risk. Table 3 shows the association between hypogonadal symptoms assessed by the ADAM questionnaire and the 10-year CVD risk. Loss of libido and less strong erection were significantly associated with an increased risk of high 10-year CVD risk [OR = 2.95 (CI 1.91–4.12) for loss of libido; OR = 3.87 (CI 2.11–4.95) for less strong erection].

Table 1. Characteristics of the 395 hypogonadal men.

Age (years)	56.1 ± 6.7
45–54 (%)	179 (45.3)
55–64 (%)	164 (41.5)
65–74 (%)	52 (13.2)
Waist (cm)	90.6 ± 7.7
Cholesterol (mg/dL)	204.5 ± 39.1
HDL (mg/dL)	43.9 ± 8.9
Hypertension (%)	210 (53.2)
DM (%)	61 (15.4)
MetS (%)	169 (42.8)
Smoking (%)	58 (14.7)
10-year CVD risk (%)	18.1 ± 11.4
Low risk (<10%)	98 (24.8)
Intermediate risk (10–20%)	166 (42.0)
High risk (≥20%)	131 (33.2)
Framingham CVD points	12.6 ± 3.8
SHBG (nmol/L)	23.3 ± 8.2
Total testosterone (ng/dL)	278.3 ± 53.5
Free testosterone (ng/dL)	6.2 ± 1.3
IIEF-5	19.4 ± 4.9
no ED (%)	86 (21.8)
Mild to moderate ED (%)	102 (25.8)
Moderate ED (%)	55 (13.9)
Severe ED (%)	44 (11.1)
Sexual inactivity (%)	108 (27.4)
Sexual frequency (per month)	2.9 ± 2.2
<1 (%)	237 (60.0)
1–3 (%)	93 (23.5)
≥4 (%)	65 (16.5)
ADAM* positive (%)	349 (88.4)
Q1	282 (71.4)
Q2	246 (62.3)
Q3	296 (74.9)
Q4	116 (29.4)
Q5	79 (20.0)
Q6	38 (9.6)
Q7	274 (69.4)
Q8	255 (64.6)
Q9	187 (47.3)
Q10	81 (21.3)

Q1. Do you have a decrease in libido (sex drive)?; Q2. Do you have a lack of energy?; Q3. Do you have a decrease in strength and/or endurance?; Q4. Have you lost height?; Q5. Have you noticed a decreased enjoyment of life?; Q6. Are you sad and/or grumpy?; Q7. Are your erections less strong?; Q8. Have you noted a recent deterioration in your ability to play sports?; Q9. Are you falling asleep after dinner?; Q10. Has there been a recent deterioration in your work performance?

*Androgen Deficiency in the Aging Male (ADAM) questionnaire.

The association was attenuated but remained significant after adjustment for age and total or free testosterone.

Discussion

The present study demonstrated that ED, low sexual frequency and decreased libido were associated with a greater CVD risk in men with low testosterone. ED and TD are interrelated in perspectives of pathophysiology and therapeutics [27]. Clinically, sexual dysfunction is the most specific symptom of late-onset hypogonadism and the primary symptoms for seeking medical treatment in aging males [20,28]. It was shown that TD and ED are both independently associated with reduced quality of life in men with type 2 diabetes mellitus, and both are considered as markers of poor health condition [29]. However, increasing evidence proves ED as a predictor or marker of CVD. It was reported that nearly 70% of coronary artery disease is preceded by ED symptoms by a mean duration of 38.8 months [30]. Several erection-related parameters, including impaired masturbation-induced erections, poor intracavernous alprostadil injection test response and flaccid penile acceleration on Doppler ultrasound, have been reported to be associated with an increased CVD risk [31–33]. Corona et al. [34] also demonstrated that penile peak systolic velocity measured in the flaccid state during color Doppler ultrasound correlates well with the value measured in the dynamic state, and the examination could identify diabetic subjects with impaired coronary flow reserve with an accuracy of 80%. In another longitudinal study, the investigators also proved that the low penile blood flow is associated with an increased risk of major cardiovascular events [35]. Therefore, there is consensus that ED represents a condition of vascular insufficiency and should be considered as an equivalent of CVD. The current study focused on men with low testosterone, which has been considered a high-risk group for CVD [8–10]. Our data confirmed the view that increased severity of ED within late-onset hypogonadism patients correlated with an increased cardiometabolic risk [36]. Another study revealed that a testosterone level <12 nmol/L was associated with an increase in cardiovascular risk, and that obesity and severe ED are the best predictors of TD-related CVD risk [37]. Moreover, the relationship between TD and CVD can be bidirectional. A recent study by Corona et al. [38] showed that hypogonadism was associated with a reduced risk of new cardiovascular events in patients with a previous history of cardiovascular events, even after adjusting for confounders. The authors concluded that hypogonadism could be interpreted as a protective mechanism in unhealthy conditions to avoid fatherhood and spare energy. Our data also confirm the necessity of screening for CVD in hypogonadal men with ED, which has proven to be a cost-effective intervention for secondary prevention of CVD [39,40].

The relationship between sexual activity and CVD has rarely been reported. It has been shown that both sex frequency and perceived importance of sexual behaviors are positively associated with quality of life [41]. An analysis of data from the Massachusetts Male Aging Study demonstrated that a low frequency of sexual activity predicts CVD independently of ED [42]. Data from the European Male Aging Study also revealed that a higher frequency of sexual activity is associated with a lower risk of CVD in their medical history [43]. Recently, Corona et al. [44] longitudinally followed a cohort of male ED patients and reported that a higher frequency of sexual intercourse significantly reduces the risk of major adverse cardiovascular events, even after adjusting for known risk factors. The current study generally confirmed the view of the above studies. Three possible mechanisms may explain the relationship between the decreased sexual frequency and the increased CVD risk. First, the frequency of sexual intercourse can be considered to be a hallmark of general health condition. Second, sexual activity itself improves cardiometabolic profiles. Third, it is also possible that the maintenance of mental, emotional, physical and relational well-being through sexual intercourse prevents cardiovascular events. It was shown that the lack of sexual activity from ED is associated with a reversible

Table 2. The odds ratios of ED and sexual frequency predicating a high 10-year CVD risk (≥20%).

	Unadjusted		Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Erectile dysfunction								
No	1.00		1.00		1.00		1.00	
Mild-moderate	2.37	(1.24, 4.51)	1.84	(1.17, 3.96)	1.67	(0.90, 3.72)	1.71	(0.87, 3.63)
Moderate	4.39	(1.78, 8.43)	3.6	(1.54, 6.72)	3.08	(1.27, 5.94)	3.64	(1.45, 6.88)
Severe	12.81	(4.65, 26.11)	8.43	(3.43, 21.67)	7.74	(2.66, 18.91)	7.91	(2.25, 17.48)
p for trend	<0.001		0.023		0.045		0.041	
Sexual frequency								
<1	1.00		1.00		1.00		1.00	
1–3	0.73	(0.43, 0.98)	0.87	(0.58, 1.29)	0.91	(0.60, 1.31)	0.88	(0.57, 1.32)
≥4	0.35	(0.23, 0.78)	0.45	(0.32, 0.80)	0.48	(0.37, 0.82)	0.51	(0.39, 1.03)
p for trend	0.011		0.013		0.021		0.023	

Model 1: adjustment for age; Model 2: adjustment for age and total testosterone; Model 3: adjustment for age and free testosterone.

Table 3. The odds ratios of hypogonadal symptoms predicating a high 10-year CVD risk (≥20%).

	Unadjusted		Model 1		Model 2		Model 3	
ADAM*	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Q1 (positive)	2.95#	(1.91, 4.12)	1.94*	(1.21, 3.41)	1.88*	(1.14, 3.11)	1.89*	(1.13, 2.96)
Q2 (positive)	1.22	(0.80, 1.88)	1.41	(0.89, 1.84)	1.33	(0.79, 1.76)	1.32	(0.78, 1.63)
Q3 (positive)	1.19	(0.74, 1.92)	1.21	(0.82, 1.73)	1.23	(0.82, 1.83)	1.13	(0.83, 1.77)
Q4 (positive)	1.05	(0.65, 1.78)	1.20	(0.72, 1.68)	1.11	(0.69, 1.56)	1.11	(0.70, 1.56)
Q5 (positive)	0.97	(0.48, 1.58)	1.04	(0.57, 1.66)	0.88	(0.39, 1.33)	0.90	(0.37, 1.42)
Q6 (positive)	1.30	(0.70, 1.98)	1.22	(0.64, 1.77)	1.05	(0.48, 1.67)	1.11	(0.59, 1.77)
Q7 (positive)	3.87#	(2.11, 4.95)	2.73#	(1.93, 4.40)	2.21*	(1.41, 3.35)	2.40*	(1.57, 3.89)
Q8 (positive)	1.34	(0.77, 2.04)	1.10	(0.61, 1.78)	0.98	(0.49, 1.48)	1.03	(0.41, 1.51)
Q9 (positive)	1.06	(0.54, 1.67)	1.21	(0.76, 1.82)	1.11	(0.45, 1.89)	1.12	(0.47, 1.79)
Q10 (positive)	0.88	(0.31, 1.34)	0.89	(0.29, 1.44)	1.03	(0.48, 1.47)	1.10	(0.51, 1.56)

Model 1: adjustment for age; Model 2: adjustment for age and total testosterone; Model 3: adjustment for age and free testosterone.
*ADAM questionnaire: listed in the legend of Table 1.
*$p < 0.05$; #$p < 0.01$.

reduction of luteinizing hormone bioavailability [45] and serum testosterone [46], and the treatment of ED with phosphodiesterase inhibitor V has been shown to enhance serum testosterone [47]. Accordingly, it has been proposed that sexual activity helps to maintain or improve general health [48]. Both the American Heart Association and the European Society of Cardiology recommend that sexual activity after acute myocardial infarction should not be delayed if the patient is able to tolerate physical activity [49,50]. However, a recent study showed that the majority of physicians give restrictions when counseling patients about resuming sexual activity after acute myocardial infarction [51]. Our data suggest that maintaining an active sexual life appears to have a beneficial effect on men's overall and cardiovascular health and that screening for sexual activity is clinically useful in hypogonadal men.

The relationship between somatic and psychological symptoms and cardiometabolic profiles has rarely been reported and remains controversial in the literature. It was shown that moderate and severe symptoms, as evaluated using the Aging Male Symptoms scale, increase the likelihood of metabolic syndrome and the cardiovascular risk [52]. However, Cunningham et al. [53] reported that free and total testosterone levels are independently associated, though modestly, with sexual desire, erectile function and sexual activity, but not vitality or physical function, as evaluated in symptomatic older men with TD. The discrepant results support the view that these hypogonadal symptoms are often not specific enough to make differential diagnosis between TD and physiological aging [54,55].

Although TD increases the risk of CVD death and all-cause mortality [8–11], some meta-analyses revealed that it is not associated with incident CVD [10,56]. Therefore, TD has been considered as a marker of poor health, rather than a specific CVD risk [10]. The current study suggests that ED, decreased sexual frequency and loss of libido can be considered as a predictor for future CVD event in the hypogonadal population. These patients should be closely monitored for their cardiovascular health, and any coexisting metabolic derangements should be properly managed. Moreover, while controversies exist regarding the effect of testosterone supplement on cardiovascular risks, a recent meta-analysis has documented that testosterone supplement did not carry any additional risk of cardiovascular events and might reduce CVD risk in subjects with metabolic diseases [14].

There are some limitations in the present study. While the Framingham Risk Scores has been widely used to calculate CVD risk, it was shown to overestimate the CVD risk in the Chinese population [57]. Recalibration using local epidemiologic data may improve the precision of the calculated CVD risk. Moreover, the current study is also limited by a relatively small number of cases. While the power is enough to establish a relationship between sexual symptoms and CVD risk, it may

be not be enough to detect the effect of somatic and psychological symptoms.

Conclusions

ED, decreased sexual frequency and loss of libido significantly predict the 10-year CVD risk in men with TD. Further prospective investigations are required in order to clarify whether improving sexual function and maintaining sexual activity can prevent CVD.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Corona G, Monami M, Rastrelli G, et al. Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med 2011;8: 272–83.
2. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol 2013;9:479–93.
3. Ho CH, Jaw FS, Wu CC, et al. The prevalence and the risk factors of testosterone deficiency in newly diagnosed and previously known type 2 diabetic men. J Sex Med 2015;12:389–97.
4. Corona G, Rastrelli G, Filippi S, et al. Erectile dysfunction and central obesity: an Italian perspective. Asian J Androl 2014;16: 581–91.
5. Corona G, Vignozzi L, Sforza A, et al. Obesity and late-onset hypogonadism. Mol Cell Endocrinol 2015;418 Pt 2:120–33.
6. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009; 30:477–94.
7. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. J Endocrinol 2013;217:R47–71.
8. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008; 93:68–75.
9. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? Trends Endocrinol Metab 2010;21:496–503.
10. Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 2011;165:687–701.
11. Araujo AB, Dixon JM, Suarez EA, et al. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96: 3007–19.
12. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050–8.
13. Muraleedharan V, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725–33.
14. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf 2014;13:1327–51.
15. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829–36.
16. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.
17. Morgentaler A, Khera M, Maggi M, Zitzmann M. Commentary: who is a candidate for testosterone therapy? A synthesis of international expert opinions. J Sex Med 2014;11:1636–45.
18. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male 2015;18:5–15.
19. Corona G, Mannucci E, Ricca V, et al. The age-related decline of testosterone is associated with different specific symptoms and signs in patients with sexual dysfunction. Int J Androl 2009;32: 720–8.
20. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35.
21. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 2014;11: 1577–92.
22. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007;92: 4241–7.
23. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
24. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metab Clin Exp 2000;49:1239–42.
25. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319–26.
26. D'Agostino Sr RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.
27. Isidori AM, Buvat J, Corona G, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment – a systematic review. Eur Urol 2014;65:99–112.
28. Shortridge EF, Polzer P, Donga P, Wade RL. Symptom report and treatment experience of hypogonadal men with and without type 2 diabetes in a United States health plan. Int J Clin Pract 2015;69: 783–90.
29. Brooke JC, Walter DJ, Kapoor D, et al. Testosterone deficiency and severity of erectile dysfunction are independently associated with reduced quality of life in men with type 2 diabetes. Andrology 2014;2:205–11.
30. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 2003;44:360–4; discussion 364–5.
31. Rastrelli G, Boddi V, Corona G, et al. Impaired masturbation-induced erections: a new cardiovascular risk factor for male subjects with sexual dysfunction. J Sex Med 2013;10:1100–13.
32. Rastrelli G, Corona G, Monami M, et al. Poor response to alprostadil ICI test is associated with arteriogenic erectile dysfunction and higher risk of major adverse cardiovascular events. J Sex Med 2011;8:3433–45.
33. Rastrelli G, Corona G, Lotti F, et al. Flaccid penile acceleration as a marker of cardiovascular risk in men without classical risk factors. J Sex Med 2014;11:173–86.
34. Corona G, Fagioli G, Mannucci E, et al. Penile Doppler ultrasound in patients with erectile dysfunction (ED): role of peak systolic velocity measured in the flaccid state in predicting arteriogenic ED and silent coronary artery disease. J Sex Med 2008;5:2623–34.
35. Corona G, Monami M, Boddi V, et al. Male sexuality and cardiovascular risk. A cohort study in patients with erectile dysfunction. J Sex Med 2010;7:1918–27.
36. Almehmadi Y, Yassin DJ, Yassin AA. Erectile dysfunction is a prognostic indicator of comorbidities in men with late onset hypogonadism. Aging Male 2015;18:186–94.
37. Martinez-Jabaloyas JM, DE-SET study group. Testosterone deficiency in patients with erectile dysfunction: when should a higher cardiovascular risk be considered? J Sex Med 2014;11: 2083–91.
38. Corona G, Rastrelli G, Maseroli E, et al. Low testosterone syndrome protects subjects with high cardiovascular risk burden from major adverse cardiovascular events. Andrology 2014;2: 741–7.
39. Pastuszak AW, Hyman DA, Yadav N, et al. Erectile dysfunction as a marker for cardiovascular disease diagnosis and intervention: a cost analysis. J Sex Med 2015;12:975–84.
40. Corona G, Giorda CB, Cucinotta D, et al. Sexual dysfunction at the onset of type 2 diabetes: the interplay of depression, hormonal and cardiovascular factors. J Sex Med 2014;11:2065–73.

41. Flynn TJ, Gow AJ. Examining associations between sexual behaviours and quality of life in older adults. Age Ageing 2015; 44:823–8.
42. Hall SA, Shackelton R, Rosen RC, Araujo AB. Sexual activity, erectile dysfunction, and incident cardiovascular events. Am J Cardiol 2010;105:192–7.
43. Corona G, Lee DM, Forti G, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). J Sex Med 2010;7: 1362–80.
44. Corona G, Rastrelli G, Monami M, et al. Frequency of sexual activity and cardiovascular risk in subjects with erectile dysfunction: cross-sectional and longitudinal analyses. Andrology 2013;1: 864–71.
45. Carosa E, Benvenga S, Trimarchi F, et al. Sexual inactivity results in reversible reduction of LH bioavailability. Int J Impot Res 2002; 14:93–9; discussion 100.
46. Jannini EA, Screponi E, Carosa E, et al. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. Int J Androl 1999;22:385–92.
47. Carosa E, Martini P, Brandetti F, et al. Type V phosphodiesterase inhibitor treatments for erectile dysfunction increase testosterone levels. Clin Endocrinol (Oxf) 2004;61:382–6.
48. Jannini EA, Fisher WA, Bitzer J, McMahon CG. Is sex just fun? How sexual activity improves health. J Sex Med 2009;6:2640–8.
49. Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2012;125:1058–72.
50. Steg PG, James SK, Atar D, Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33: 2569–619.
51. Lindau ST, Abramsohn EM, Bueno H, et al. Sexual activity and counseling in the first month after acute myocardial infarction among younger adults in the United States and Spain: a prospective, observational study. Circulation 2014;130:2302–9.
52. Garcia-Cruz E, Leibar-Tamayo A, Romero-Otero J, et al. Marked testosterone deficiency-related symptoms may be associated to higher metabolic risk in men with low testosterone levels. J Sex Med 2014;11:2292–301.
53. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. J Clin Endocrinol Metab 2015;100:1146–55.
54. Corona G, Rastrelli G, Vignozzi L, et al. How to recognize late-onset hypogonadism in men with sexual dysfunction. Asian J Androl 2012;14:251–9.
55. Bernie AM, Scovell JM, Ramasamy R. Comparison of questionnaires used for screening and symptom identification in hypogonadal men. Aging Male 2014;17:195–8.
56. Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart 2011;97:870–5.
57. Liu J, Hong Y, D'Agostino Sr RB, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591–9.