REVIEW

Men's Health: Sexual Dysfunction, Physical, and Psychological Health—Is There a Link?

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ABSTRACT

Introduction. Sexual dysfunction in men, such as erectile dysfunction, hypogonadism, and premature ejaculation, generates considerable attention. Its association with physical and psychological health is an issue which should be addressed seriously.

Aim. A review of the literature pertaining to the correlation between sexual dysfunction and physical and psychological health.

Methods. PubMed search for relevant publications on the association between sexual dysfunction in men and physical and psychological health.

Main Outcome Measure. Clinical and epidemiological evidence that demonstrates the association between sexual dysfunction in men and physical and psychological health.

Results. Sexual dysfunction, i.e., erectile dysfunction, hypogonadism, and premature ejaculation, has been shown to be associated with physical and psychological health. There is a strong correlation between sexual dysfunction and cardiovascular disease, metabolic syndrome, quality of life, and depression.

Conclusion. The association between men's sexual dysfunction and physical and psychological health is real and proven. Therefore, it should not be taken lightly but instead treated as a life-threatening medical problem. **Tan HM, Tong SF, and Ho CCK. Men's health: Sexual dysfunction, physical, and psychological health—Is there a link? J Sex Med 2012;9:663–671.**

Key Words. Health; Physical; Psychological; Sexual Dysfunction

Introduction

Sexual health is defined as a state of physical, emotional, mental, and social well-being related to sexuality. It is not merely an absence of disease, dysfunction, or infirmity, and it requires a positive and respectful approach to sexuality and sexual relationship [1]. Sexual dysfunction in men encompasses erectile dysfunction, testosterone deficiency (hypogonadism), and ejaculatory disorders, particularly premature ejaculation. With aging of the world population, the prevalence of sexual dysfunction, particularly erectile dysfunction, is projected to increase markedly.

About 100 million men worldwide are affected by erectile dysfunction, and this is expected to increase to 322 million in 2025 [2]. Similarly, men's serum testosterone decline progressively after the age of 40 [3–5]. The prevalence of adult males with low serum testosterone (total testosterone <10.4 nmol/L or 300 ng/dL) ranges from 10–25% [6]. However, prevalence of symptomatic androgen deficiency in adult male is around 10% [7]. In the Global Study of Sexual Attitudes and Behaviors, which surveyed the various aspects of sexual health among adults aged 40–80 years in 29 countries, the overall prevalence rate for premature ejaculation was 30% [8].

Despite the availability of effective treatment for erectile dysfunction, testosterone deficiency, and premature ejaculation, a large group of men affected by sexual dysfunction are not receiving appropriate treatment [8]. It might be due to the skepticism of the relationship between sexual dysfunction and their overall health. In this review, we would like to explore the current evidence for the relationship between psychological and physical health.

Methods

We conducted a literature search using PubMed from 1970 to 2010. The following Medical Subject Heading terms were used: "sexual dysfunction," "erectile dysfunction," "hypogonadism;" and "men" or "male;" and "quality of life" or "mental health" or "chronic disease" or "mortality" or "morbidity" or "epidemiology". This was supplemented by key words search using the following terms and their synonyms: "sexual health," "testosterone deficiency," "cardiovascular risk," "non communicable disease," "diabetes," "hypertension," "obesity," and "stroke". Inclusion criteria for article selection were: articles in English, studies (of any design) on sexual dysfunction in men, and publication in a peer-reviewed journal. The abstracts and full text of the articles, identified from the initial search, were reviewed by two authors independently, who subsequently reached a consensus on adding each included article. The reference lists of identified articles were reviewed manually for additional relevant articles. Additional studies, recommended by expert peer reviewers, were examined and added.

Sexual Dysfunction and Quality of Life (QoL)

Many studies have shown that sexual dysfunction and QoL are closely interrelated [9–15]. Men bothered by sexual problem were more likely to have lower overall life satisfaction scores, mental health QoL scores, and vitality QoL scores. Perceived physical health was also found to be independently associated with sexual satisfaction and various sexual problems. Specifically, erectile dysfunction is the main male sexual problem associated with mental health QoL [9].

Sexual problems have also been attributed to other physical, clinical, and psychological factors [10,16]. Patients with erectile dysfunction had been shown to have significant adverse effects on both physical and mental health dimension of QoL [12,13].

Sexual Dysfunction and Physical Health

Many recent publications have clearly demonstrated that physical health is associated with sexual health. Numerous epidemiological studies have revealed a strong correlation between erectile dysfunction and cardiovascular risk factors that include hypertension, dyslipidemia, diabetes, and obesity [17–24].

Consistently, high prevalence of erectile dysfunction has been reported in men with comorbidities like cardiovascular disease, hypertension, diabetes, and stroke [25–29]. Similarly, men with erectile dysfunction are more likely to report having comorbid medical conditions [30–32]. In the original Men's Attitudes to Life Events and Sexuality (MALES) and Asian MALES studies, the prevalence for cardiovascular disease and diabetes were two to three times higher in men with erectile dysfunction compared with men without erectile dysfunction [30,32].

Current knowledge supports the notion that erectile dysfunction is a sentinel marker for cardiovascular disease and stroke [26,33–40]. This is attributed mainly to shared pathophysiological mechanism and arterial occlusion [33,37,41–46] and common risk factors [47–51]. It is believed that progressive occlusive disease should manifest early in smaller vessels in the penile bed before involving larger coronary vessels [20,37,38]. Further, the penile arteries are end arteries and are thus less able to compensate for decrease blood flow as does in the heart and brain. As such, patients with a recent onset of erectile dysfunction often do not complain of symptoms of cardiovascular disease, and patients with cardiovascular disease commonly give a history of preceding erectile dysfunction [20]. Erectile dysfunction can therefore be considered an early marker for cardiovascular risk and preclinical cardiovascular disease [52].

Many studies have revealed that obesity, i.e., high body mass index was associated with prevalence and progression of erectile dysfunction, indicating that obesity is a risk factor for cardiovascular disease [53,54]. Further, a study on the intervention of obese men aged 33–55 years revealed that reduction of $\geq$10% of baseline body weight over 2 years correlated with a significant improvement in erectile function, resulting in reduction of cardiovascular risk [55].

The pioneering work of Thompson et al. showed prospectively a group of asymptomatic, healthy men who had, or developed, erectile dysfunction and then subsequently developed cardiovascular events [21]. This strong association between erectile dysfunction and subsequent development of cardiovascular events and risk of cardiovascular mortality is further confirmed by the Olmsted County Study and the Massachusetts Male Aging Study (MMAS) cohort study [56,57]. Erectile dysfunction was also shown to predict multiple end points of various adverse cardiac events in both low [21,58] and high [59,60] cardiovascular risk population. The Thompson Prostate Cancer Prevention Trial study showed that in the 40–69 years age group, men with erectile dysfunction have about a twofold greater risk of cardiovascular disease than men without erectile dysfunction [21]. The Olmsted Country Study on community dwelling men showed that erectile dysfunction was associated with about 80% higher risk of subsequent coronary artery disease, especially in the younger age group [56].

In the MMAS prospective study that followed 40–70 year old men for 15 years, erectile dysfunction was positively associated with all causes of mortality and cardiovascular mortality in age and multivariate adjusted models [57]. Men with erectile dysfunction had a 26% higher risk of all-cause mortality and a 43% higher risk of death due to cardiovascular disease compared with men without erectile dysfunction. Erectile dysfunction was found to be comparable with a number of conventional risk factors such as hypertension, diabetes, and self-assessment of health [57]. In this study, erectile dysfunction was however not associated with other causes of mortality like cancer mortality.

The findings from these three key studies have major clinical and public health implications especially in the promotion of men's health. The advent of effective oral medications for treatment of erectile dysfunction has prompted a huge population of men to seek treatment, providing the primary care physicians an opportunity to predict, detect, and treat men for cardiometabolic disease (cardiovascular disease and diabetes). The reported prevalence of silent coronary artery disease in patients with erectile dysfunction, ranged between 8% and 56% [20,60]. This observation is also supported by a study by Mulhall et al. showing men with vasculogenic erectile dysfunction had between six- to tenfold increased incidences of abnormal stress echocardiogram [61].

As 66% of sudden cardiac deaths and 20% of nonsudden cardiac deaths occur in patients without a history of coronary artery disease, and the fact that 70% of all erectile dysfunction is vascular in origin, physicians should pay particular attention to all men presenting with erectile dysfunction [62,63]. Furthermore, a large scale study of 25,650 men revealed a 75% increase risk of peripheral vascular disease in men with preexisting erectile dysfunction [64]. Often, the appearance of erectile dysfunction precedes symptomatic cardiovascular diseases by 1 to 5 years [21]. Educating and impressing men on the link between erectile dysfunction and cardiometabolic disease will motivate men to adhere to lifestyle modifications in primary and secondary prevention of the diseases.

Current knowledge has clearly shown the close association between erectile dysfunction and cardiometabolic disease and risk factors. This link is particularly strong for men above 50 years of age and with existing cardiovascular risk factors. There is still a large population of younger and healthy men with symptoms suggestive of organic erectile dysfunction of long duration and yet current cardiovascular assessments do not show any abnormalities [65]. There is definitely a need to conduct studies to detect subtle or early abnormalities of the penile vasculature both hemodynamically and biochemically. Confirmation of any physiological or biochemical disarrangement is vital to instill prophylactic or preventive measures.

The other common conditions affecting men's sexual health are testosterone deficiency and premature ejaculation. Testosterone deficiency is a clinical and biochemical syndrome, frequently associated with age and comorbidities. It may affect the function of many bodily systems resulting in significant decline in the QoL including sexual dysfunction [66].

The clinical manifestations of testosterone deficiency are variable. Sexual dysfunctions like hypoactive sexual desire, erectile dysfunction, and delayed ejaculations are prominent presenting symptoms [67]. Other presenting features that affect physical health and QoL include visceral obesity, diminished muscle mass, muscle strength, bone mineral density, and alterations in spatial cognitions and mood [66]. Observational studies, both cross-sectional and prospective cohort studies, have revealed that testosterone deficiency is frequently associated with metabolic diseases [68–80]. Low testosterone is significantly associated with obesity (relative risk 2.38), type 2 diabetes (relative risk 2.1), metabolic syndrome and its

components, and insulin resistance [68–70]. The triad consisting of erectile dysfunction, metabolic syndrome, and testosterone deficiency is very prevalent and commonly reported [71–73]. Many cohort studies have shown that low testosterone levels predict type 2 diabetes and metabolic syndrome. Similarly, obesity, type 2 diabetes, and metabolic syndrome predict subsequent testosterone deficiency [77–80]. A meta-analysis by Isidori and colleagues revealed favorable results of testosterone replacement therapy with respect to decline in total fat mass and improvement in lean body mass [81].

Testosterone has been widely accepted as detrimental to the cardiovascular system. However, numerous epidemiological studies have suggested otherwise [82]. Nearly all epidemiological studies have revealed that high testosterone is not associated with cardiovascular disease [82]. The majority of studies have shown that testosterone level is inversely related to most cardiovascular risk factors and degree of atherosclerosis [82]. A majority of cohort studies revealed no correlation between testosterone levels and subsequent cardiovascular morbidity or mortality [82]. However, at least three recent studies have suggested significant correlations between low testosterone levels and either cardiovascular or all-cause mortalities [83–85]. Of concern to us are sporadic cohort studies that have reported weak but definite correlation between androgen levels and cardiovascular mortality [86–88]. More long-term, large scale, prospective randomized controlled trials of testosterone therapy looking at cardiovascular parameters and mortalities are urgently needed.

Premature ejaculation, which affects 30% of men in all age groups, is still a very stigmatized and distressing medical condition. Premature ejaculation is quoted as the most common sexual problem, and it is threefold more prevalent than erectile dysfunction in men below 40 years of age [10]. Current knowledge on premature ejaculation as a genuine organic sexual dysfunction related to serotonin dysregulation [89,90] and its association with medical conditions like prostatitis, chronic pelvic pain syndrome, varicocoele, and thyroid disease [91–93] provide both physicians and patients, especially in the younger age group, an excellent platform to engage in health consultation and promotions. The advent of effective oral medication, specifically designed for premature ejaculation, and the dissemination of awareness of this common distressing sexual problems will provide a legitimate opportunity for men to seek medical consultation.

Sexual Dysfunction and Psychological Health

Besides QoL and physical health, sexual dysfunction is also related to psychological health. Depression is often seen in men with sexual dysfunction. In a study in Malaysia, men with erectile dysfunction had significantly higher geriatric depression scores compared with men without erectile dysfunction; i.e., a higher proportion of men with erectile dysfunction suffered from depression [94]. In Japan, it was shown that the odds ratio for an association between erectile dysfunction and depression was 2.02 [95]. In a cross-national study between Brazil, Italy, Japan, and Malaysia, depression was shown to be associated with erectile dysfunction in a graded manner, and men with erectile dysfunction were 2.09 times more likely to have depression [96].

In the study by Araujo et al., the estimated odds ratio for erectile dysfunction was 1.82 in the presence of depressive symptoms. What was more important was that they showed that this relationship between depressive symptoms and erectile dysfunction was independent of important aging and para-aging confounders, such as demographic, anthropometric and lifestyle factors, health status, medication use, and hormones [97]. Besides depression itself, antidepressant medication use also may cause erectile dysfunction. Conversely, it has also been shown that erectile dysfunction independently may cause or exacerbate depressive moods [98].

The diagnosis of depression among erectile dysfunction patients is affected by the manner by which it is diagnosed. When Strand et al. used categorical diagnosis such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), only a small number of erectile dysfunction patients were noted to be depressed. However, when measured dimensionally using the Brief Symptom Inventory, significant elevations of depression and other dysphoric affects were revealed. This demonstrates an important fact that men with erectile dysfunction are affectively distressed but infrequently meet the criteria for categorical DSM-IV depression [99].

Hypogonadism is also associated with depression. Levels of testosterone have been shown to be lower in depressed patients than in nondepressed individuals [100–104]. This relationship between low levels of testosterone and depression is more obvious in aging men. Elderly men who have depression or dysthymic disorder appear to have lower testosterone levels compared with nonde-

pressed elderly men [105–112]. Decreased testosterone levels were also seen in patients with schizophrenia who present with a depressive episode [113–115]. In a study in Asia, 30% of the hypogonadal men were found to have mild/moderate depression whereas 9.37% had severe depression [116]. This relationship between hypogonadism and depression is further strengthened by a systematic review and meta-analysis that concluded testosterone therapy may have an antidepressant effect in depressed patients, especially those with hypogonadism [117].

Serum testosterone level in the body is also greatly influenced by an individual's emotional state. A sustained reduction in testosterone secretion can occur when faced with life stresses such as those caused by work or relationships. Positive emotional states on the other hand, will increase testosterone production [118]. Sleep deprivation has also been shown to cause low testosterone levels [119].

For premature ejaculation, the association with mental health was confirmed in a recent study from Malaysia, where the Hospital Anxiety and Depression Scale (HADS) was used to measure the psychological impact. In this study, the odds of having anxiety and depression among men with premature ejaculation were 2.83 (95% CI = 1.45–5.54) and 2.08 (95% CI = 0.97–4.44), respectively. It was also noted that the higher the HADS score, the higher was the prevalence of premature ejaculation. The prevalence of premature ejaculation was 13.6%, 41.5%, and 68.6% in those with low (0–7), medium (8–10), or high (>11) HADS scores, respectively [120].

Conclusion

Awareness of erectile dysfunction, testosterone deficiency, and premature ejaculation has increased substantially, and discussion on these issues between patients and health professionals is more open, less stigmatized, and easier to initiate, especially if the discussion is contextualized and confined to serious medical diseases. Men's sexual dysfunction including testosterone deficiency syndrome should be highlighted as not just QoL but also as life-threatening issues.

Primary care physicians should be aware of the various sexual dysfunction issues and their relationship to various life-threatening medical conditions and diseases. In the promotion and maintenance of men's health, the front line physicians should focus on age-specific clinical evaluation and provide the appropriate preventive or interventional measures.

There is a need for screening for all sexual dysfunction men for their physical as well as psychological health. Public health authorities also have a role in creating awareness by disseminating knowledge on this issue. Men's sexual health across all age groups is indeed intimately related to men's physical and mental health.

There is also a need for further research on the association of cardiovascular risks among young, healthy men with symptoms of erectile dysfunction. Research to detect subtle or early abnormalities of the penile vasculature both hemodynamically and biochemically will help in the formulation of prophylactic and preventive measures. Besides that, more robust, long-term, large scale, prospective randomized controlled trials of testosterone therapy looking at cardiovascular parameters and mortalities are urgently needed to confirm the benefits and safety of testosterone therapy. The association between premature ejaculation and physical health is another area that needs to be addressed.

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References

1 World Health Organization. Defining sexual health. Report of a technical consultation on sexual health 28–31 January 2002, Geneva. WHO: Geneva 2006, 5pp. Available at http://www.who.int/reproductivehealth/publications/sexual_health/defining_sexual_health.pdf (accessed January 15, 2011).

2 Aytac IA, Mckinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy conquences. BJU Int 1999;84:50–6.

3 Tan HM, Marumo K, Yang DY, Hwang TI, Ong ML. Sex among Asian men and women: The Global Better Sex Survey in Asia. Int J Urol 2009;16:507–14.

4 Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54–61.

5 Corona G, Lee DM, Forti G, O'Connor DB, Maggi M, O'Neill TW, Pendleton N, Bartfai G, Boonen S, Casanueva FF, Finn JD, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Punab M, Silman AJ, Vanderschueren D, Wu FC, the EMAS Study Group. 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.

6 Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S. Testosterone and estradiol among older men. J Clin Endocrinol Metab 2006;91:1336–44.

7 Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007;92:4241–7.

8 Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO, GSSAB Investigators' Group. Sexual behaviour and dysfunction and help-seeking patterns in adults aged 40–80 years in the urban population of Asian countries. BJU Int 2005;95:609–14.

9 Lau JT, Kim JH, Tsui HY. Prevalence of male and female sexual problems, perceptions related to sex and association with quality of life in a Chinese population: A population-based study. Int J Impot Res 2005;17:494–505.

10 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. JAMA 1999;281:537–44.

11 Sánchez-Cruz JJ, Cabrera-León A, Martín-Morales A, Fernández A, Burgos R, Rejas J. Male erectile dysfunction and health-related quality of life. Eur Urol 2003;44:245–53.

12 Fujisawa M, Sawada K, Okada H, Arakawa S, Saito S, Kamidono S. Evaluation of health-related quality of life in patients treated for erectile dysfunction with viagra (sildenafil citrate) using SF-36 score. Arch Androl 2002;48:15–21.

13 Giuliano F, Peña BM, Mishra A, Smith MD. Efficacy results and quality-of-life measures in men receiving sildenafil citrate for the treatment of erectile dysfunction. Qual Life Res 2001;10:359–69.

14 Litwin MS, Nied RJ, Dhanani N. Health-related quality of life in men with erectile dysfunction. J Gen Intern Med 1998;13:159–66.

15 Olfson M, Uttaro T, Carson WH, Tafesse E. Male sexual dysfunction and quality of life in schizophrenia. J Clin Psychiatry 2005;66:331–8.

16 Incrocci L, Slob AK, Levendag PC. Sexual (dys)function after radiotherapy for prostate cancer: A review. Int J Radiat Oncol Biol Phys 2002;52:681–93.

17 Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, McKinlay JB. Erectile dysfunction and coronary risk factors: Prospective results from the Massachusetts Male Aging Study. Prev Med 2000;30:328–38.

18 Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. Am J Epidemiol 1994;140:930–7.

19 Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology 2004;64:1196–201.

20 Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, Rigatti P, Montorsi F. The artery size hypothesis: A macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol 2005;96:19M–23M.

21 Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. JAMA 2005;294:2996–3002.

22 El-Sakka AI. Association of risk factors and medical comorbidities with male sexual dysfunctions. J Sex Med 2007;4:1691–700.

23 Mulhall J, Teloken P, Brock G, Kim E. Obesity, dyslipidemias and erectile dysfunction: A report of a subcommittee of the sexual medicine society of North America. J Sex Med 2006;3:778–86.

24 Sun P, Cameron A, Seftel A, Shabsigh R, Niederberger C, Guay A. Erectile dysfunction—An observable marker of diabetes mellitus? A large national epidemiological study. J Urol 2006;176:1081–5.

25 Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic coronary artery disease. Am J Cardiol 2003;91:230–1.

26 Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, Galli S, Ravagnani PM, Montorsi P. 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.

27 Burchardt M, Burchardt T, Anastasiadis AG, Kiss AJ, Shabsigh A, de La Taille A, Pawar RV, Baer L, Shabsigh R. Erectile dysfunction is a marker for cardiovascular complications and psychological functioning in men with hypertension. Int J Impot Res 2001;13:276–81.

28 Korpelainen JT, Kauhanen ML, Kemola H, Malinen U, Myllylä VV. Sexual dysfunction in stroke patients. Acta Neurol Scand 1998;98:400–5.

29 Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet 1985;1:181–4.

30 Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M, Men's Attitudes to Life Events and Sexuality (MALES) Study. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin 2004;20:607–17.

31 Khoo EM, Tan HM, Low WY. Erectile dysfunction and comorbidities in aging men: An urban cross-sectional study in Malaysia. J Sex Med 2008;5:2925–34.

32 Tan HM, Low WY, Ng CJ, Chen KK, Sugita M, Ishii N, Marumo K, Lee SW, Fisher W, Sand M. Prevalence and correlates of erectile dysfunction (ED) and treatment seeking for ED in Asian men: The Asian Men's Attitudes to Life Events and Sexuality (MALES) study. J Sex Med 2007;4:1582–92.

33 Billups KL. Sexual dysfunction and cardiovascular disease: Integrative concepts and strategies. Am J Cardiol 2005;96:57M–61M.

34 Billups KL, Bank AJ, Padma-Nathan H, Katz SD, Williams RA. Erectile dysfunction as a harbinger for increased cardiometabolic risk. Int J Impot Res 2008;20:236–42.

35 Greenstein A, Chen J, Miller H, Matzkin H, Villa Y, Braf Z. Does severity of ischemic coronary disease correlate with erectile function? Int J Impot Res 1997;9:123–6.
36 Montorsi P, Ravagnani PM, Galli S, Rotatori F, Veglia F, Briganti A, Salonia A, Dehò F, Rigatti P, Montorsi F, Fiorentini C. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: The COBRA trial. Eur Heart J 2006;27:2632–9.
37 Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, Dehò F, Montorsi F. Common grounds for erectile dysfunction and coronary artery disease. Curr Opin Urol 2004;14:361–5.
38 Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol 2003;44:352–4.
39 Morley JE, Korenman SG, Kaiser FE, Mooradian AD, Viosca SP. Relationship of penile brachial pressure index to myocardial infarction and cerebrovascular accidents in older men. Am J Med 1988;84:445–8.
40 Ponholzer A, Temml C, Obermayr R, Wehrberger C, Madersbacher S. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? Eur Urol 2005;48: 512–8.
41 Ganz P. Erectile dysfunction: Pathophysiologic mechanisms pointing to underlying cardiovascular disease. Am J Cardiol 2005;96:8M–12M.
42 Guay AT. ED2: Erectile dysfunction = endothelial dysfunction. Endocrinol Metab Clin North Am 2007;36:453–63.
43 Guay AT. Relation of endothelial cell function to erectile dysfunction: Implications for treatment. Am J Cardiol 2005;96:52M–6M.
44 Jones RW, Rees RW, Minhas S, Ralph D, Persad RA, Jeremy JY. Oxygen free radicals and the penis. Expert Opin Pharmacother 2002;3:889–97.
45 Maas R, Schwedhelm E, Albsmeier J, Böger RH. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. Vasc Med 2002;7:213–25.
46 Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: Endothelial dysfunction is the common denominator. Heart 2003;89:251–3.
47 Rosen RC, Wing R, Schneider S, Gendrano N 3rd. Epidemiology of erectile dysfunction: The role of medical comorbidities and lifestyle factors. Urol Clin North Am 2005;32: 403–17.
48 Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: Results from the health professionals follow-up study. Ann Intern Med 2003;139:161–8.
49 Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. A prospective study of risk factors for erectile dysfunction. J Urol 2006;176:217–21.
50 Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: Can lifestyle changes modify risk? Urology 2000;56:302–6.
51 Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: The Rancho Bernardo study. J Am Coll Cardiol 2004;43:1405–11.
52 Jackson G, Rosen RC, Kloner RA, Kostis JB. The second Princeton consensus on sexual dysfunction and cardiac risk: New guidelines for sexual medicine. J Sex Med 2006;3:28–36.
53 Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The natural progression and remission of erectile dysfunction: Results from the Massachusetts Male Aging Study. J Urol 2007;177:241–6.
54 Tan HM, Ng CJ, Low WY, Khoo EM, Yap PK, Tan WS. The Subang Men's Health research—A multiethnic community based study. Aging Male 2007;10:111.
55 Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D. Effect of lifestyle changes on erectile dysfunction in obese men: A randomized controlled trial. JAMA 2004;291:2978–84.
56 Inman BA, Sauver JL, Jacobson DJ, McGree ME, Nehra A, Lieber MM, Roger VL, Jacobsen SJ. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 2009;84:108–13.
57 Araujo AB, Travison TG, Ganz P, Chiu GR, Kupelian V, Rosen RC, Hall SA, McKinlay JB. Erectile dysfunction and mortality. J Sex Med 2009;6:2445–54.
58 Schouten BW, Bohnen AM, Bosch JL, Bernsen RM, Deckers JW, Dohle GR, Thomas S. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: Results from the Krimpen Study. Int J Impot Res 2008;20:92–9.
59 Gazzaruso C, Solerte SB, Pujia A, Coppola A, Vezzoli M, Salvucci F, Valenti C, Giustina A, Garzaniti A. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: A potential protective role for statins and 5-phosphodiesterase inhibitors. J Am Coll Cardiol 2008;51:2040–4.
60 Gazzaruso C, Giordanetti S, De Amici E, Bertone G, Falcone C, Geroldi D, Fratino P, Solerte SB, Garzaniti A. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. Circulation 2004;110:22–6.
61 Mulhall J, Teloken P, Barnas J. Vasculogenic erectile dysfunction is a predictor of abnormal stress echocardiography. J Sex Med 2009;6:820–5.
62 Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
63 Goldstein I. Male sexual circuitry. Working Group for the Study of Central Mechanisms in Erectile Dysfunction. Sci Am 2000;283:70–5.
64 Blumentals WA, Gomez-Caminero A, Joo S, Vannappagari V. Is erectile dysfunction predictive of peripheral vascular disease? Aging Male 2003;6:217–21.
65 Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. J Am Coll Cardiol 2004;43:179–84.
66 Brawer MK. Testosterone replacement in men with andropause: An overview. Rev Urol 2004;6(suppl 6):S9–15.
67 Buvat J, Maggi M, Gooren L, Guay AT, Kaufman J, Morgentaler A, Schulman C, Tan HM, Torres LO, Yassin A, Zitzmann M. Endocrine aspects of male sexual dysfunctions. J Sex Med 2010;7:1627–56.
68 Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: The HIM study. Int J Clin Pract 2006;60: 762–9.
69 Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic

syndrome in aging men. J Clin Endocrinol Metab 2005; 90:2618–23.
70 Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? J Urol 2006;176(Pt 1):1524–7.
71 Corona G, Mannucci E, Schulman C, Petrone L, Mansani R, Cilotti A, Balercia G, Chiarini V, Forti G, Maggi M. Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol 2006;50:595–604.
72 Guay A, Jacobson J. The relationship between testosterone levels, the metabolic syndrome (by two criteria), and insulin resistance in a population of men with organic erectile dysfunction. J Sex Med 2007;4(Pt 1):1046–55.
73 Shabsigh R, Katz M, Yan G, Makhsida N. Cardiovascular issues in hypogonadism and testosterone therapy. Am J Cardiol 2005;96:67M–72M.
74 Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: Prospective results from the Massachusetts Male Aging Study. Diabetes Care 2000;23:490–4.
75 Oh JY, Barrett-Connor E, Wedick NM, Wingard DL, Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo study. Diabetes Care 2002;25:55–60.
76 Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036–41.
77 Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, Andres R. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab 2007;92:3568–72.
78 Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen JT. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: A prospective cohort study. J Clin Endocrinol Metab 2005;90:712–9.
79 Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones:the Massachusetts Male Ageing Study. Clin Endocrinol (Oxf) 2006;65:125–31.
80 Travison TG, O'Donnell AB, Araujo AB, Matsumoto AM, McKinlay JB. Cortisol levels and measures of body composition in middle-aged and older men. Clin Endocrinol (Oxf) 2007;67:71–7.
81 Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A. Effects of testosterone on sexual function in men: Results of a meta-analysis. Clin Endocrinol (Oxf) 2005;63:381–94.
82 Wu FC, von Eckardstein A. Androgens and coronary artery disease. Endocr Rev 2003;24:183–217.
83 Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A, Day N. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694–701.
84 Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008;93:68–75.
85 Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660–5.
86 Araujo AB, Kupelian V, Page ST, Handelsman DJ, Bremner WJ, McKinlay JB. Sex steroids and all-cause and cause-specific mortality in men. Arch Intern Med 2007;167:1252–60.
87 Maggio M, Lauretani F, Ceda GP, Bandinelli S, Basaria S, Ble A, Egan J, Paolisso G, Najjar S, Jeffrey Metter E, Valenti G, Guralnik JM, Ferrucci L. Association between hormones and metabolic syndrome in older Italian men. J Am Geriatr Soc 2006;54:1832–8.
88 Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: Prospective evidence from the Caerphilly study. Circulation 2005;112:332–40.
89 Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: The involvement of the serotonergic system. Behav Brain Res 1998;92:111–8.
90 Giuliano F. 5-Hydroxytryptamine in premature ejaculation: Opportunities for therapeutic intervention. Trends Neurosci 2007;30:79–84.
91 Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. Urology 2001;58:198–202.
92 Xing JP, Fan JH, Wang MZ, Chen XF, Yang ZS. [Survey of the prevalence of chronic prostatitis in men with premature ejaculation]. Zhonghua Nan Ke Xue 2003;9:451–3.
93 Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, Jannini EA. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab 2005;90:6472–9.
94 Low WY, Khoo EM, Tan HM, Hew FL, Teoh SH. Depression, hormonal status and erectile dysfunction in the aging male: Results from a community study in Malaysia. J Mens Health Gend 2006;3:263–70.
95 Sugimori H, Yoshida K, Tanaka T, Baba K, Nishida T, Nakazawa R, Iwamoto T. Relationships between erectile dysfunction, depression and anxiety in Japanese subjects. J Sex Med 2005;2:390–6.
96 Nicolosi A, Moreira E, Villa M, Glasser D. A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men. J Affect Disord 2003;82:235–43.
97 Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: Cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 1998;60:458–65.
98 Shiri R, Koskimäki J, Tammela TL, Häkkinen J, Auvinen A, Hakama M. Bidirectional relationship between depression and erectile dysfunction. J Urol 2007;177:669–73.
99 Strand J, Wise TN, Fagan PJ, Schmidt CW Jr. Erectile dysfunction and depression: Category or dimension? J Sex Marital Ther 2002;28:175–81.
100 Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiology and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl 1992;13:297–304.
101 Baischer W, Koinig G, Hartmann B, Huber J, Langer G. Hypothalamic-pituitary-gonadal axis in depressed premenopausal women: Elevated blood testosterone concentrations compared to normal controls. Psychoneuroendocrinology 1995;20:553–9.
102 Osran H, Reist C, Chen CC, Lifrak ET, Chicz-DeMet A, Parker LN. Adrenal androgens and cortisol in major depression. Am J Psychiatry 1993;150:806–9.
103 Seidman SN, Walsh BT. Testosterone and depression in aging men. Am J Geriatr Psychiatry 1999;7:18–33.
104 Sachar EJ, Halpern F, Rosenfeld RS, Galligher TF, Hellman L. Plasma and urinary testosterone levels in depressed men. Arch Gen Psychiatry 1973;28:15–8.

105 Delhez M, Hansenne M, Legros JJ. Andropause and psychopathology: Minor symptoms rather than pathological ones. Psychoneuroendocrinology 2003;28:863–74.
106 Margolese HC. The male menopause and mood: Testosterone decline and depression in the aging male—Is there a link? J Geriatr Psychiatry Neurol 2000;13:93–101.
107 Seidman SN, Araujo AB, Roose SP, Devanand DP, Xie S, Cooper TB, McKinlay JB. Low testosterone levels in elderly men with dysthymic disorder. Am J Psychiatry 2002;159: 456–9.
108 Rubin RT, Poland RE, Lesser IM. Neuroendocrine aspects of primary endogenous depression. VIII. Pituitary-gonadal axis activity in male patients and matched control subjects. Psychoneuroendocrinology 1989;14:217–29.
109 Seidman SN. Testosterone deficiency and mood in aging men: Pathogenic and therapeutic interactions. World J Biol Psychiatry 2003;4:14–20.
110 Waltman C, Blackman MR, Chrousos GP, Riemann C, Harman SM. Spontaneous and glucocorticoid-inhibited adrenocorti-cotropic hormone and cortisol secretion are similar in healthy young and old men. J Clin Endocrinol Metab 1991;73:495–502.
111 Vermeulen A, Kaufman JM. Ageing of the hypothalamopituitary-testicular axis in men. Horm Res 1995;43:25–8.
112 Yoshida NM, Kumano H, Kuboki T. Does the aging males' symptoms scale assess major depressive disorder?: A pilot study. Maturitas 2006;53:171–5.
113 Kaneda Y. Possible relationship between testosterone and comorbid major depressive episode in male patients with schizophrenia treated with typical antipsychotic medications. Clin Neuropharmacol 2003;26:291–3.
114 Ozcan ME, Banoglu R. Gonadal hormones in schizophrenia and mood disorders. Eur Arch Psychiatry Clin Neurosci 2003;253:193–6.
115 Mason JW, Giller EL, Kosten TR. Serum testosterone differences between patients with schizophrenia and those with affective disorder. Biol Psychiatry 1988;23:357–66.
116 Low WY, Khoo EM, Tan HM. Hypogonadal men and their quality of life. Aging Male 2007;10:77–87.
117 Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: Systematic review and meta-analysis. J Psychiatr Pract 2009;15:289–305.
118 Friedl KE, Moore RJ, Hoyt RW, Marchitelli LJ, Martinez-Lopez LE, Askew EW. Endocrine markers of semistarvation in healthy lean men in a multistressor environment. J Appl Physiol 2000;88:1820–30.
119 Tyyskä J, Kokko J, Salonen M, Koivu M, Kyröläinen H. Association with physical fitness, serum hormones and sleep during a 15-day military field training. J Sci Med Sport 2010;13:356–9.
120 Quek KF, Sallam AA, Ng CH, Chua CB. Prevalence of sexual problems and its association with social, psychological and physical factors among men in a Malaysian population: A cross-sectional study. J Sex Med 2008;5:70–6.