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Cardiovascular diseases and erectile dysfunction: the two faces of the coin of androgen deficiency

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Summary

Traditionally, clinical conditions synonymous with the ageing male included cardiovascular disease (CVD), type 2 diabetes mellitus (DM) and sexual dysfunction, and were widely regarded as independent clinical entities. Over the last decade, interrelationship of clinical conditions has been convincingly demonstrated. Declining testosterone levels in the elderly, once regarded as an academic endocrinological question, appear to be central to the listed pathologies. It is now clear that erectile dysfunction is an expression of endothelial dysfunction. Testosterone deficiency is associated with an increased incidence of CVD and DM. The latter is often the sequel of the metabolic syndrome. Visceral obesity, a pivotal characteristic of the metabolic syndrome, suppresses the hypothalamic–pituitary–testicular axis leading to diminished testosterone production. Conversely, substantial androgen deficiency leads to signs and symptoms of metabolic syndrome. It is erroneous not to include testosterone measurements in the progress of the CVD, DM and erectile dysfunction. These conditions correlate strongly with testosterone deficiency.

British Medical Journal had a venerable tradition of publishing in their end-of-the year issues scientifically robust research whereas, at the same time, amazing and amusing their readership. In December 20, 1997 issue of the British Medical Journal, Davey Smith *et al.* (1997) published a study with the title 'Sex and death: are they related? Findings from the Caerphilly cohort study'. The study concluded that mortality risk was 50% lower in the group with high orgasmic frequency than in the group with low orgasmic frequency, with evidence of a dose–response relation across the groups. Whereas death from coronary heart disease and from other causes showed similar associations with frequency of orgasm, the gradient was most marked for deaths from coronary heart disease.

A decade later we are able to offer some perspectives on this association which was difficult to interpret in 1997. It is not far fetched to assume that the men with the highest frequency of orgasm were – statistically speaking – those who were least bothered by erectile dysfunction. Now a host of studies indicate that erectile function and dysfunction are reliable telltales of cardiovascular health in a bi-directional fashion: the quality of erectile function is a reflection of the health of the cardiovascular system and CVD is almost inevitably associated with degrees of erectile dysfunction.

Erectile dysfunction and CVD: two faces of the same coin

Erectile dysfunction (ED) is a local penile expression of generalised vascular pathology with the underlying pathology being endothelial dysfunction. Endothelial dysfunction, which manifests itself clinically as impaired vasodilatation is the hallmark of ED. The endothelium is the single layer of cells lining the surface of blood vessels.

It has become clear that it is not merely a histological structure but it has several important functions in cardiovascular health and disease with regard to vascular tone, inflammation and adhesion of thrombocytes. The process of arteriosclerosis starts at the endothelium (Nacci *et al.*, 2009).

The vascular endothelium is pivotal for vasodilatation which is the physiological basis for adequate tissue perfusion to warrant adequate oxygenation in relation to actual demands. This flexible response depends on the capacity to change the resistance of the vascular system. The underlying physiological mechanism is the production of local agents of which the most significant is nitric oxide (NO). It inhibits platelet aggregation and regulates vascular tone (Nacci *et al.*, 2009). Bioavailable NO can be increased by enhancing its production or reducing its inactivation. NO induces endothelial vasodilatation by increasing the cGMP content of vascular smooth muscle cells, resulting in relaxation. Cardiac risk factors – including dyslipidaemia, hypertension and type 2 diabetes – are all associated with impaired endothelial function (Nacci *et al.*, 2009; Potenza *et al.*, 2009). Evidence is accumulating that ED is an early sign of CVD (El-Sakka & Morsy, 2004; El-Sakka *et al.*, 2004). ED is an important marker of vascular disease throughout the arterial tree (Jackson, 2009).

The Massachusetts Male Aging Study (MMAS), a random-sample cohort study of men aged 40–70, investigated the relationship between baseline risk factors for coronary heart disease and subsequent ED, on the assumption that subclinical arterial disease might be manifested as ED (Feldman *et al.*, 2000). Overweight [body mass index (BMI): > 28 kg m^{-2}] and a composite coronary risk score also significantly predicted incident ED (Feldman *et al.*, 2000). Cardiovascular risk factors in mid-life could predict the incidence of ED an average of 25 years later. A study which assessed seven classic CHD risk factors in men aged 30–69 from 1972 to 1974 and then again in 1998, found that mean age, BMI, cholesterol and triglycerides were each significantly associated with an increased risk of ED (Fung *et al.*, 2004).

Erectile function is viewed by almost all men as a significant component of quality of life (Holden *et al.*, 2005) and erectile difficulties (ED) may be a reason to seek medical advice. As indicated above, several studies document now that there is a high concordance between the causes of ED and the causes of CVD, this indirectly by demonstrating that there is an elevated prevalence of the metabolic syndrome and insulin resistance in a population of men with ED as compared with a general population of men (Bansal *et al.*, 2005). The authors argue that the ultimate goal therefore must be not only to treat the erectile problem but also to diagnose and adequately (aggressively) treat any cardiac risk factors that may be found.

The Massachusetts Male Aging Study equally revealed that erectile dysfunction was predictive of the metabolic syndrome. This study supports the idea that erectile dysfunction may provide a warning sign and, at the same time, an opportunity for early intervention in men otherwise considered at lower risk for the metabolic syndrome and subsequent CVD (Kupelian *et al.*, 2006b).

The MMAS has also estimated the frequency of erectile dysfunction progression and remission among ageing men, and assessed the relation of progression/remission to demographics, socioeconomic factors, comorbidities and modifiable lifestyle characteristics (Travison *et al.*, 2007). Natural remission and progression occur in a substantial number of men with erectile dysfunction. Age and BMI were associated with progression and remission of ED. Interventions were nonpharmacological which apparently impacted on remission and delaying progression of ED. The association of BMI with remission and progression, and the association of smoking and health status with progression, offer potential avenues for facilitating remission and delaying progression using nonpharmacological intervention. Lifestyle changes are associated with improvement in sexual function in about one-third of obese men with erectile dysfunction at baseline. Weight loss and increased physical activity appeared to have a favourable effect on erectile and endothelial functions in obese men (Esposito *et al.*, 2004a,b).

The benefits of such interventions for overall men's health may be far-reaching and support the view that ED is a portal to men's health.

Shabsigh *et al.* (2008a,b) have eloquently argued that ED can calculate men's health risks. Elements in the calculation of health risks (hypertension, diabetes, angina or hyperlipidaemia) in men presenting with ED are health status on a scale of 1–7 (1 = excellent, 7 = poor), waist size, severity of ED, presence/absence of a sexual partner. The calculation produces scores within the range of 1–7. If the score is 1.5–2.5 = medium risk (30–59% probability); ≥ 2.5 = high risk (≥60% probability of having the condition) and <1.5 = low risk (<30% probability) (Shabsigh *et al.*, 2008b). A study with a similar message was conveyed by Corona *et al.* (2008).

The coin of androgen deficiency

Androgens and sexual functioning

As the title indicates, this review addresses erectile dysfunction and CVD as the two faces of the coin of androgen deficiency. This has recently authoritatively been reviewed (Traish *et al.*, 2009a).

When Professor Vermeulen from Ghent, Belgium started his pioneering work on the decline of testosterone levels in old age in the 1970s, his work seemed to most professionals of theoretical interest only (for review: Kaufman & Vermeulen, 2005). Now, 30–40 years later, the pathophysiological implications of the decline, not rarely amounting to testosterone deficiency, have become clear. The understanding of the (patho)physiological functions of testosterone with regard to sexual functioning has undergone a revolutionary development. A decline in testicular function with a consequent decline in testosterone level is recognised as a common occurrence in older men (Morales, 2003; El-Sakka & Hassoba, 2006). It was well-known that hypogonadism in men usually results in loss of libido and potency which can be restored by androgen administration. The original insights into the mechanisms of action of androgens on sexual function indicated a prominent role of testosterone on sexual interest whereas the effects of testosterone on erectile function were less apparent from these early investigations (Bancroft & Wu, 1983). But new research has presented convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity, at least in part reversible upon androgen replacement (Shabsigh, 2004; Gooren & Saad, 2006; Traish *et al.*, 2007; Buvat & Bou Jaoude, 2008). There are androgen receptors in the human corpus cavernosum (Aversa *et al.*, 2003). Several studies show that testosterone plays a critical role in restoring and maintaining the penile trabecular smooth muscle structure and function (Traish *et al.*, 1999, 2003; Yassin & Saad, 2005) as well as regulating the cell apoptosis (Shabsigh, 1997). In line with this, Aversa *et al.* (2000) reported that the circulating levels of free testosterone, independently of age, positively correlated with the degree of relaxation of the corporal smooth muscle cells and the cavernous endothelial cells, giving support to the potential role of androgens in regulating smooth muscle function in the penis.

Adipocyte accumulation in penile subtunical area of the corpus cavernosum emphasised the potential mechanism for veno-occlusive dysfunction in androgen deficiency (Traish *et al.*, 2005) (for review: Gooren & Saad, 2006). A study of Corona *et al.* (2009b) shows that pulse pressure as an index of arterial stiffness is associated with androgen deficiency and impaired penile blood flow in men with ED. Testosterone has a positive impact on haemodynamic processes and the veno-occlusive properties in the penile trabecular tissues. Testosterone may repair venous leakage in hypogonadal patients and subjects with metabolic syndrome. The impact of a hormonal factor on veno-occlusive properties of the corpora cavernosa indicates that restoration of testosterone to normal may repair mechanical damage of the corpora cavernosa (Yassin & Saad, 2006; Yassin *et al.*, 2006b; Kurbatov *et al.*, 2008). This has also been found to be the case in laboratory animals.

In a well-designed intervention study Aversa *et al.* (2003) provided support for this mechanism of action of testosterone on the erectile tissues of the penis. They assessed the effects of androgen administration in 20 patients with arteriogenic ED (confirmed with dynamic colour duplex ultrasound), not responding to treatment with sildenafil 100 mg. The patients' testosterone levels were in the lower quartile of the normal range. In this placebo-controlled study, treatment with transdermal testosterone raised plasma testosterone levels and led to an increase of arterial inflow into the cavernous tissue and to an improvement of ED thus enhancing the response to treatment with PDE-5-inhibitors. In line with the above Foresta *et al.* (2004) have documented that normal plasma testosterone is required for erectile function. In severely hypogonadal men (plasma testosterone < 2.0 ng ml^{-1}) the nocturnal penile tumescence, ultrasound measurement of arterial carvernous inflow and visually stimulated erection in response to sildenafil 50 mg or apomorphine 3 mg were minimal. The responses to these pharmacological stimuli normalised after 6 months of administration of testosterone patches evidencing the significant role of normal levels of testosterone for erectile function.

The phosphodiesterase type 5 inhibitors (PDE5-Is) have revolutionised treatment of erectile dysfunction (ED). But 30–35% of patients fail to respond. Associated testosterone deficiency, not properly diagnosed, has been proposed as one of the reasons for failure. A number of studies suggest that the activity of PDE5-Is as a treatment of ED is androgen-dependent. In rodents castration reduces protein expression and activity of PDE5, and testosterone treatment is capable of upregulation (Traish *et al.*, 1999; Morelli *et al.*, 2004). In addition medical or surgical castration prevents the enhancing effect of PDE5-Is on erections induced by electrostimulation of the cavernous nerves (Traish *et al.*, 1999; Zhang *et al.*, 2005). The expression of NO synthesis (Azadzoi *et al.*, 1992; Burnett, 2004) is regulated by androgens. The expression of PDE5 has been found to be androgen-dependent as well in humans (Morelli *et al.*, 2004). In addition, several clinical studies suggest that testosterone deficiency is a risk factor for poor response to sildenafil (Guay *et al.*, 2001; 2003; Park *et al.*, 2005; Rosenthal *et al.*, 2006; Koulikov *et al.*, 2007; Teloken *et al.*, 2007; Traish *et al.*, 2007). Five uncontrolled studies have also reported beneficial effects of a combination therapy with testosterone and PDE5-Is in men with ED and low or low-normal testosterone who previously had not responded to 100 mg sildenafil (Shabsigh, 2004;

Shamloul *et al.*, 2005; Hwang *et al.*, 2006; Rosenthal *et al.*, 2006) or 20 mg tadalafil (Yassin *et al.*, 2006a).

In a well-designed randomised placebo-controlled trial, Rochira *et al.* (2006) demonstrated that sildenafil is able to restore nocturnal erections of men with almost undetectable levels of testosterone to the same extent as testosterone replacement therapy though the combination was more powerful than either alone.

Androgens and (risk factors of) CVD

Until a decade ago, it was widely regarded that androgens have an atherogenic effect and thus led to CVD, and androgen administration was thought to contribute to the development of CVD. Over the last decade, several papers have examined the relationship of androgens with CVD and concluded that it is no longer tenable to regard testosterone as a culprit in the aetiology of CVD (Liu *et al.*, 2003; Wu & von Eckardstein, 2003; Jones *et al.*, 2005; Shabsigh *et al.*, 2005, 2006; Jones & Saad (2009), unpublished data). Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men (Shores *et al.*, 2004, 2006; Khaw *et al.*, 2007; Maggio *et al.*, 2007; Laughlin *et al.*, 2008).

Over the last 2 years a large number of review papers have highlighted the significance of depressed levels of testosterone and CVD (Corona *et al.*, 2008, 2009a; Yassin *et al.*, 2008; Traish *et al.*, 2009b).

Both cross-sectional and longitudinal epidemiological studies have convincingly established that low plasma testosterone/low SHBG are correlated with/predict the metabolic syndrome (Laaksonen *et al.*, 2003a; Blouin *et al.*, 2005; Kalme *et al.*, 2005; Muller *et al.*, 2005; Kupelian *et al.*, 2006a). Numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone (Allan *et al.*, 2006, 2007; Kaplan *et al.*, 2006; Mohr *et al.*, 2006; Kalyani & Dobs, 2007; Rodriguez *et al.*, 2007). There is an inverse relationship between waist circumference, a reliable indicator of visceral obesity and testosterone levels over all age groups (Svartberg *et al.*, 2004).

Adiposity with its associated hyperinsulinism suppresses SHBG synthesis and therewith the levels of circulating testosterone (Eckel *et al.*, 2005; Kaufman & Vermeulen, 2005). It also may affect the strength of LH signalling to the testis (Lima *et al.*, 2000). Further, insulin (Pitteloud *et al.*, 2005) and leptin (Isidori *et al.*, 1999) have a suppressive effect on testicular steroidogenesis. Visceral fat cells secrete a large number of cytokines which impair testicular steroidogenesis (Lyon *et al.*, 2003; Trayhurn & Wood, 2004; Eckel *et al.*, 2005). Thus, there are reasons to believe that adiposity is a significant factor in lowering circulating levels of testosterone. While it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome, suppresses circulating testosterone levels, it has also been documented that low testosterone induces the metabolic syndrome (Stellato *et al.*, 2000; Laaksonen *et al.*, 2004). Low testosterone and SHBG levels appeared strongly associated not only with components of the metabolic syndrome, but also with the metabolic syndrome itself, independently of BMI. Furthermore, sex hormones were associated with inflammation and body iron stores. Even in the absence of late-stage consequences such as diabetes and CVD, subtle derangements in sex hormones are present in the metabolic syndrome, and may contribute to its pathogenesis (Laaksonen *et al.*, 2003b).

The relative contributions of each of the individual National Cholesterol Education Program Adult Treatment Panel III components of the metabolic syndrome to low serum testosterone in ageing men have been examined using multiple linear regression modelling. Based on these analyses the presence of diabetes or fasting serum glucose greater than 110 mg dl^{-1}, BMI 30 kg m^{-2} or greater, and triglycerides 150 mg dl^{-1} or greater each appeared to have a clinically relevant association with low serum testosterone (Kaplan, 2006). El-Sakka *et al.* (2008) have recently demonstrated significant associations between low level of total testosterone and DHEA-S and poor control of diabetes. Furthermore, they have reported that there were significant associations between control of diabetes and normal levels of total testosterone at 3- and 6-months follow-up visits (El-Sakka *et al.*, 2009).

The role of testosterone is dramatically demonstrated by findings in men with prostate cancer who undergo androgen ablation therapy (Basaria *et al.*, 2006; Smith & Nathan, 2006), particularly in the longer-term (Brag-Basaria *et al.*, 2006). Another study showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men (Yialamas *et al.*, 2007) and strongly impairs glycaemic control of men with DM (Haidar *et al.*, 2007).

Conclusion

Until a decade ago the ailments of elderly men, such as atherosclerosis, hypertension, DM, lower urinary tract symptoms and erectile dysfunction, were regarded as distinct diagnostic/therapeutic entities but there is a growing recognition that these entities are not disparate but interdependent in their aetiology. To improve the health of the ageing male, they require an integral diagnostic and therapeutic approach. Measurement of testosterone is pivotal to adequate health care in most of the ailments of ageing men. While this may be obvious in cases of ED, it should include conditions such as CVD and DM2. This

may at first seem unorthodox to physicians treating patients with these conditions.

References

Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI (2006) The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men. *Med J Aust* 185:424–427.

Allan CA, Strauss BJ, McLachlan RI (2007) Body composition, metabolic syndrome and testosterone in ageing men. *Int J Impotence Res* 19:448–457.

Aversa A, Isidori AM, De Martino MU, Caprio M, Fabbrini E, Rocchietti-March M, Frajese G, Fabbri A (2000) Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. *Clin Endocrinol (Oxf)* 53:517–522.

Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A (2003) Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol (Oxf)* 58:632–638.

Azadzoi KM, Kim N, Brown ML, Goldstein I, Cohen RA, Saenz de Tejada I (1992) Endothelium-derived nitric oxide and cyclooxygenase products modulate corpus cavernosum smooth muscle tone. *J Urol* 147:220–225.

Bancroft J, Wu FC (1983) Changes in erectile responsiveness during androgen replacement therapy. *Arch Sex Behav* 12:59–66.

Bansal TC, Guay AT, Jacobson J, Woods BO, Nesto RW (2005) Incidence of metabolic syndrome and insulin resistance in a population with organic erectile dysfunction. *J Sex Med* 2:96–103.

Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS (2006) Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer* 106:581–588.

Blouin K, Despres JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A (2005) Contribution of age and declining androgen levels to features of the metabolic syndrome in men. *Metabolism* 54:1034–1040.

Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S (2006) Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 24:3979–3983.

Burnett A (2004) Novel nitric oxide signaling mechanisms regualte the erectile response. *Int J Impot Res* 16:15–19.

Buvat J, Bou Jaoude G (2008) Combination therapy with phosphodiesterase type V inhibitors and testosterone. *Curr Sex Health Rep* 5:135–140.

Corona G, Forti G, Maggi M (2008) Why can patients with erectile dysfunction be considered lucky? The association with testosterone deficiency and metabolic syndrome *Aging Male* 11:193–199.

Corona G, Mannucci E, Forti G, Maggi M (2009a) Hypogonadism, ED, metabolic syndrome and obesity: a pathological link supporting CVDs. *Int J Androl* 32:74–80.

Corona G, Mannucci E, Lotti F, Fisher AD, Bandini E, Balercia G, Forti G, Maggi M (2009b) Pulse pressure, an index of arterial stiffness, is associated with androgen deficiency and impaired penile blood flow in men with ED. *J Sex Med* 6:285–293.

Davey Smith G, Frankel S, Yarnell J (1997) Sex and death: are they related? Findings from the Caerphilly cohort study *BMJ Clin Res Ed* 315:1641–1644.

Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. *Lancet* 365:1415–1428.

El-Sakka AI, Hassoba HM (2006) Age-related testosterone depletion in patients with erectile dysfunction. *J Urol* 176:2589–2593.

El-Sakka AI, Morsy AM (2004) Screening for ischemic heart disease in patients with erectile dysfunction: role of penile Doppler ultrasonography. *Urology* 64:346–350.

El-Sakka AI, Morsy AM, Fagih BI, Nassar AH (2004) Coronary artery risk factors in patients with erectile dysfunction. *J Urol* 172:251–254.

El-Sakka AI, Sayed HM, Tayeb KA (2008) Diabetes-associated androgen alteration in patients with erectile dysfunction. *Int J Androl* 31:602–608.

El-Sakka AI, Sayed HM, Tayeb KA (2009) Androgen pattern in patients with II diabetes-associated erectile dysfunction: Impact of metabolic control. *Urology*, 74: 552–560.

Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D (2004a) Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 291:2978–2984.

Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D (2004b) Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 292:1440–1446.

Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, McKinlay JB (2000) Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med* 30:328–338.

Foresta C, Caretta N, Rossato M, Garolla A, Ferlin A (2004) Role of androgens in erectile function. *J Urol* 171:2358–2362. quiz 2435.

Fung MM, Bettencourt R, Barrett-Connor E (2004) Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo study. *J Am Coll Cardiol* 43:1405–1411.

Gooren LJ, Saad F (2006) Recent insights into androgen action on the anatomical and physiological substrate of penile erection. *Asian J Androl* 8:3–9.

Guay AT, Perez JB, Jacobson J, Newton RA (2001) Efficacy and safety of sildenafil citrate for treatment of erectile

dysfunction in a population with associated organic risk factors. *J Androl* 22:793–797.

Haidar A, Yassin A, Saad F, Shabsigh R (2007) Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male* 10:189–196.

Holden CA, McLachlan RI, Pitts M, Cumming R, Wittert G, Agius PA, Handelsman DJ, de Kretser DM (2005) Men in Australia Telephone Survey (MATeS): a national survey of the reproductive health and concerns of middle-aged and older Australian men. *Lancet* 366:218–224.

Hwang TI, Chen HE, Tsai TF, Lin YC (2006) Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. *Int J Impot Res* 18: 400–404.

Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A (1999) Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab* 84:3673–3680.

Jackson G (2009) Sexual response in CVD. *J Sex Res* 46:233–236.

Jones TH, Saad F (2009) The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process. *Atherosclerosis.* (unpublished data).

Jones RD, Nettleship JE, Kapoor D, Jones HT, Channer KS (2005) Testosterone and atherosclerosis in aging men: purported association and clinical implications. *Am J Cardiovasc Drugs* 5:141–154.

Kalme T, Seppala M, Qiao Q, Koistinen R, Nissinen A, Harrela M, Loukovaara M, Leinonen P, Tuomilehto J (2005) Sex hormone-binding globulin and insulin-like growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. *J Clin Endocrinol Metab* 90:1550–1556.

Kalyani RR, Dobs AS (2007) Androgen deficiency, diabetes, and the metabolic syndrome in men. *Curr Opin Endocrinol Diabetes Obes* 14:226–234.

Kaplan SA, Meehan AG, Shah A (2006) 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* 176:1524–1527. discussion 1527–1528.

Kaufman JM, Vermeulen A (2005) The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 26:833–876.

Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A, Day N (2007) Endogenous testosterone and mortality due to all causes, CVD, and cancer in men. European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 116: 2694–2701

Koulikov D, Fridmans A, Chertin B, Shenfeld O, Farkas A, Spitz IM (2007) Is sildenafil citrate associated with an amelioration of the symptomatology of androgen decline in the aging male? *J Urol* 177:2267–2271.

Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB (2006a) Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *J Clin Endocrinol Metab* 91:843–850.

Kupelian V, Shabsigh R, Araujo AB, O'Donnell AB, McKinlay JB (2006b) Erectile dysfunction as a predictor of the metabolic syndrome in aging men: results from the Massachusetts male aging study. *J Urol* 176:222–226.

Kurbatov D, Kuznetsky J, Traish A (2008) Testosterone improves erectile function in hypogonadal patients with venous leakage. *J Androl* 29:630–637.

Laaksonen DE, Kainulainen S, Rissanen A, Niskanen L (2003a) Relationships between changes in abdominal fat distribution and insulin sensitivity during a very low calorie diet in abdominally obese men and women. *Nutr Metab Cardiovasc Dis* 13:349–356.

Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT (2003b) Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol* 149:601–608.

Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT (2004) Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 27:1036–1041.

Laughlin GA, Barrett-Connor E, Bergstrom J (2008) Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 93:68–75.

Lima N, Cavaliere H, Knobel M, Halpern A, Medeiros-Neto G (2000) Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat. *Int J Obes Relat Metab Disord* 24:1433–1437.

Liu PY, Death AK, Handelsman DJ (2003) Androgens and CVD. *Endocr Rev* 24:313–340.

Lyon CJ, Law RE, Hsueh WA (2003) Minireview: adiposity, inflammation and atherogenesis. *Endocrinology* 144:2195–2200.

Maggio M, Lauretani F, Ceda GP, Bandinelli S, Ling SM, Metter EJ, Artoni A, Carassale L, Cazzato A, Ceresini G, Guralnik JM, Basaria S, Valenti G, Ferrucci L (2007) Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study. *Arch Intern Med* 167:2249–2254.

Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB (2006) The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts male aging study. *Eur J Endocrinol* 155:443–452.

Morales A (2003) An integral view of the neuroendocrine aspects of male sexual dysfunction and aging. *Can J Urol* 10:1777–1779.

Morelli A, Filippi S, Mancina R, Luconi M, Vignozzi L, Marini M, Orlando C, Vannelli GB, Aversa A, Natali A, Forti G, Giorgi M, Jannini EA, Ledda F, Maggi M (2004) Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology* 145:2253–2263.

Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT (2005) Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab* 90:2618–2623.

Nacci C, Tarquinio M, Montagnani M (2009) Molecular and clinical aspects of endothelial dysfunction in diabetes. *Intern Emerg Med* 4:107–116.

Park K, Ku JH, Kim SW, Paick JS (2005) Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. *BJU Int* 95:366–370.

Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, Hayes FJ (2005) Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab* 90:2636–2641.

Potenza MA, Gagliardi S, Nacci C, Carratu MR, Montagnani M (2009) Endothelial dysfunction in diabetes: from mechanisms to therapeutic targets. *Curr Med Chem* 16:94–112.

Rochira V, Balestrieri A, Madeo B, Granata AR, Carani C (2006) Sildenafil improves sleep-related erections in hypogonadal men: evidence from a randomized, placebo-controlled, crossover study of a synergic role for both testosterone and sildenafil on penile erections. *J Androl* 27:165–175.

Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, Andres R (2007) Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. *J Clin Endocrinol Metab* 92: 3568–3572

Rosenthal BD, May NR, Metro MJ, Harkaway RC, Ginsberg PC (2006) Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. *Urology* 67:571–574.

Shabsigh R (1997) The effects of testosterone on the cavernous tissue and erectile function. *World J Urol* 15:21–26.

Shabsigh R (2004) Testosterone therapy in erectile dysfunction. *Aging Male* 7:312–318.

Shabsigh R, Katz M, Yan G, Makhsida N (2005) Cardiovascular issues in hypogonadism and testosterone therapy. *Am J Cardiol* 96:67M–72M.

Shabsigh R, Rajfer J, Aversa A, Traish AM, Yassin A, Kalinchenko SY, Buvat J (2006) The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract* 60:1087–1092.

Shabsigh R, Arver S, Channer KS, Eardley I, Fabbri A, Gooren L, Heufelder A, Jones H, Meryn S, Zitzmann M (2008a) Sexual health as a portal to men's health: a problem turned around into an opportunity. *Int J Clin Pract* 62:179–181.

Shabsigh R, Shah M, Sand M (2008b) Erectile dysfunction and men's health: developing a comorbidity risk calculator. *J Sex Med* 5:1237–1243.

Shamloul R, Ghanem H, Fahmy I, El-Meleigy A, Ashoor S, Elnashaar A, Kamel I (2005) Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. *J Sex Med* 2:559–564.

Shores MM, Moceri VM, Gruenewald DA, Brodkin KI, Matsumoto AM, Kivlahan DR (2004) Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in a geriatric rehabilitation unit. *J Am Geriatr Soc* 52:2077–2081.

Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR (2006) Low serum testosterone and mortality in male veterans. *Arch Intern Med* 166:1660–1665.

Smith RMLH, Nathan DM (2006) Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 91:1305–1308.

Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB (2000) Testosterone, sex hormone-binding globulin, and the development of II diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care* 23:490–494.

Svartberg J, von Muhlen D, Sundsfjord J, Jorde R (2004) Waist circumference and testosterone levels in community dwelling men. The Tromso study. *Eur J Epidemiol* 19:657–663.

Teloken PE, Ohebshalom M, Mohideen N, Mulhall JP (2007) Analysis of the impact of androgen deprivation therapy on sildenafil citrate response following radiation therapy for prostate cancer. *J Urol* 178:2521–2525.

Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I (1999) Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology* 140:1861–1868.

Traish AM, Munarriz R, O'Connell L, Choi S, Kim SW, Kim NN, Huang YH, Goldstein I (2003) Effects of medical or surgical castration on erectile function in an animal model. *J Androl* 24:381–387.

Traish AM, Toselli P, Jeong SJ, Kim NN (2005) Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency. *J Androl* 26:242–248.

Traish AM, Goldstein I, Kim NN (2007) Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. *Eur Urol* 52:54–70.

Traish AM, Guay A, Feeley R, Saad F (2009a) The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. *J Androl* 30:10–22.

Traish AM, Saad F, Guay A (2009b) The dark side of testosterone deficiency: II. II diabetes and insulin resistance. *J Androl* 30:23–32.

Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB (2007) The natural progression and remission of erectile dysfunction: results from the Massachusetts male aging study. *J Urol* 177:241–246.

Trayhurn P, Wood IS (2004) Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 92:347–355.

Wu FC, von Eckardstein A (2003) Androgens and coronary artery disease. *Endocr Rev* 24:183–217.

Yassin AA, Saad F (2005) Modulation of erectile function with long acting testosterone injection (Nebido) i.m. in hypogonadal patients. *Int J Androl* 28 (Suppl. 1):53 (abstract).

Yassin AA, Saad F (2006) Dramatic improvement of penile venous leakage upon testosterone administration. A case report and review of literature. *Andrologia* 38:34–37.

Yassin AA, Saad F, Diede HE (2006a) Testosterone and erectile function in hypogonadal men unresponsive to tadalafil: results from an open-label uncontrolled study. *Andrologia* 38:61–68.

Yassin AA, Saad F, Traish A (2006b) Testosterone undecanoate restores erectile function in a subset of patients with venous leakage: a series of case reports. *J Sex Med* 3:727–735.

Yassin AA, Saad F, Gooren LJ (2008) Metabolic syndrome, testosterone deficiency and erectile dysfunction never come alone. *Andrologia* 40:259–264.

Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ (2007) Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 92:4254–4259.

Zhang XH, Morelli A, Luconi M, Vignozzi L, Filippi S, Marini M, Vannelli GB, Mancina R, Forti G, Maggi M (2005) Testosterone regulates PDE5 expression and *in vivo* responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol* 47:409–416. discussion 416.