Testosterone deficiency in the aging male

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***Abstract*:** Treatment for hypogonadism is on the rise, particularly in the aging population. Yet treatment in this population represents a unique challenge to clinicians. The physiology of normal aging is complex and often shares the same, often vague, symptoms of hypogonadism. In older men, a highly prevalent burden of comorbid medical conditions and polypharmacy complicates the differentiation of signs and symptoms of hypogonadism from those of normal aging, yet this differentiation is essential to the diagnosis of hypogonadism. Even in older patients with unequivocally symptomatic hypogonadism, the clinician must navigate the potential benefits and risks of treatment that are not clearly defined in older men. More recently, a greater awareness of the potential risks associated with treatment in older men, particularly in regard to cardiovascular risk and mortality, have been appreciated with recent changes in the US Food and Drug Administration recommendations for use of testosterone in aging men. The aim of this review is to provide a framework for the clinician evaluating testosterone deficiency in older men in order to identify correctly and treat clinically significant hypogonadism in this unique population while minimizing treatment-associated harm.

Keywords: androgens, erectile dysfunction, hormones, hypogonadism, testosterone

Introduction

Testosterone has become one of the most widely prescribed medications in the USA, increasing five-fold according to 2011 data. This increase has resulted in the dramatic growth of the testosterone replacement therapy (TRT) sector of the pharmaceutical industry from US$18 million in the 1980s to US$1.6 billion in 2011 [Handelsman, 2013]. The reason is multifactorial, but can partly be attributed to the continued growth of the population over 65 years of age and a greater awareness of medical comorbidities more prevalent with age and associated with low testosterone, such as metabolic syndrome (MetS) and cardiovascular disease (CVD) [Traish *et al.* 2009a, 2009b].

Testosterone levels also decrease with age as rapidly as 0.4–2% annually after age 30 years [Harman *et al.* 2001; Kaufman and Vermeulen, 2005; Wu *et al.* 2008], with 35% of men in the seventh decade having lower testosterone levels than younger men [Vermeulen and Kaufman, 1995], and 13% of older age men meeting diagnostic levels for hypogonadism [Araujo *et al.* 2007; Zarotsky *et al.* 2014]. This has led to the emergence of a group of men older than age 65 years with hypogonadism deemed 'late-onset' hypogonadism (LOH) or andropause, one of many synonyms.

Accurate characterization of this group of men with LOH is particularly difficult since the symptoms of hypogonadism are often nonspecific compared with the expected symptoms of aging [McGill *et al.* 2012]. Furthermore, the benefits and risks of treatment in this group are even less defined, leading to several important controversies. The US Food and Drug Administration (FDA) issued a statement in March 2015 stating that exogenous testosterone should not be used for hypogonadism due only to aging without a 'defined cause', broadly stated as a 'disorder of the testicles, pituitary gland, or brain resulting in hypogonadism'. Such language suggests that a population of aging men with symptomatic hypogonadism due to identifiable causes exists in whom consideration for treatment is warranted. Therefore, the key to evaluation is moving away from the terminology of 'LOH' and attempting to

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identify whether a truly pathophysiologic issue is involved. In addition, because the risks of TRT in this population are higher than in younger men, the risk profile of TRT becomes a driving force in the decision to treat or observe. The aim of this review is to describe the pathophysiology and physical diagnosis of symptomatic hypogonadism in the aging population, as well as to discuss the benefits, risks, and controversies of TRT for this unique patient population.

Etiologies of hypogonadism in aging men

Testosterone has a critical role in the modulation of adult male reproductive health, sexual function, bone health, fat metabolism, and muscle mass and strength. Testosterone production by testicular Leydig cells is closely regulated by the hypothalamic–pituitary–gonadal (HPG) axis *via* production of luteinizing hormone (LH). Failure in this delicate balance can result in primary, secondary, or mixed hypogonadism. Once produced, testosterone circulates systemically either protein bound or unbound. Approximately 20–25% is loosely protein bound to albumin and can uncouple to join free serum testosterone (1–2%), making 'bioavailable' free testosterone [Manni *et al.* 1985]. The remainder is tightly protein bound by sex hormone-binding globulin (SHBG) and is physiologically inactive [Rosner, 1991]. Biologically active testosterone can then bind androgen-binding protein within Sertoli cells to maintain intratesticular testosterone for spermatogenesis [Jarow *et al.* 2001], convert to more potent androgens in nontesticular tissue such as dihydrotestosterone *via* 5α-reductase enzyme, or convert to estrogen *via* aromatase enzyme. Testosterone, other androgens, estrogen, and inhibin from Sertoli cells all serve as negative feedback to gonadotropin secretion [Hayes *et al.* 2001].

Older men can suffer from well-known causes of primary hypogonadism as seen in younger men. Primary hypogonadism is classically diagnosed by laboratory testing in symptomatic men revealing hypergonadotropic hypogonadism with low serum testosterone levels and elevated LH, suggesting testicular dysfunction or failure. Common causes of hypogonadism include: prior treatment for testicular cancer, prior testicular infection, medications with gonadotoxic effects including chemotherapy, environmental toxins, orchiectomy, trauma, idiopathic testicular atrophy, genetic aberrations such as Klinefelter's syndrome, or anatomic abnormalities such as varicoceles [McBride *et al.* 2015]. Varicoceles are known to cause intratesticular dysfunction and have a higher prevalence in men with increasing age [Canales *et al.* 2005]. Recent data have not only correlated varicoceles with low testosterone but also suggest improvement in testosterone levels with repair [Tanrikut *et al.* 2011]. In general, etiologies of primary hypogonadism should be considered for treatment regardless of patient age.

In contrast to primary hypogonadism, secondary hypogonadism typically presents with hypogonadotropic hypogonadism due to insufficient gonadotropin production. In addition to being associated with numerous medical conditions and medications discussed below, primary gonadotropin-releasing hormone (GNRH) deficiency such as Kallmann syndrome, hypopituitarism from prior radiation, infection, trauma, or hyperprolactinemia from pituitary adenomas can all cause secondary hypogonadism and should be considered for treatment.

In aging men, the predominant form of testosterone deficiency (TD) is mixed with primary and secondary hypogonadism components, due to several reasons. LH levels can vary in older men based upon decreased numbers and function of Leydig cells, decreased sensitivity of the HPG axis to feedback inhibition, and/or decreased LH pulse amplitude despite normal pulse frequency. Decreased LH pulse amplitude may potentially be related to reductions in neuronal cell secretion of GNRH [Vermeulen and Kaufman, 1995; Kaufman and Vermeulen, 2005]. Total serum testosterone levels also decrease with age, but the greatest decrease is seen with bioavailable testosterone, which can be reduced by 50% by age 75 [Vermeulen *et al.* 1996]. This fall in bioavailable testosterone is due to rising SHBG levels with aging, which explains the disproportion between total and bioavailable testosterone levels. In addition to aging, SHBG levels are also increased with chronic disease states such as hyperthyroidism, cirrhosis, and HIV. Diurnal variation in testosterone levels related to pulsatile release of gonadotropins by the HPG axis results in peak serum testosterone levels during morning hours. Aging can blunt diurnal variation [Bremner *et al.* 1983], but fluctuating serum testosterone levels can also be affected by laboratory assay differences in sensitivity, seasonality, triglyceride levels, glucose ingestion, or activity prior to serum laboratory draw [Smith *et al.* 2013; Paduch *et al.* 2014]. However, a proportion of older men with low afternoon testosterone levels can have normal

morning levels [Brambilla *et al.* 2007; Crawford *et al.* 2007].

A number of possible comorbid medical conditions may accentuate these age-related, physiologic alterations in serum testosterone levels resulting in secondary or mixed hypogonadism. It is important in the current medical climate for the clinician to identify a contributing pathologic etiology other than only age-related decreases in serum testosterone to warrant treatment. MetS, defined by the International Diabetes Federation as central obesity, hypertriglyceridemia, low high-density lipid cholesterol, hypertension, or insulin resistance, has been highly associated with TD and low SHBG levels [Cunningham, 2015], in up to 50–70% of patients [Vermeulen *et al.* 1993; Wu *et al.* 2010]. Possible underlying mechanisms include hyperinsulinemia causing suppression of SHBG synthesis [Hautanen, 2000], hyperleptinemia-mediated inhibition of the HPG axis [Isidori *et al.* 1999], hyperestrogenemia-mediated gonadotropin inhibition [Maggio *et al.* 2010], and circulating inflammatory cytokine inhibition of Leydig-cell function [Bornstein *et al.* 2004]. In fact, a recent meta-analysis including four prospective studies demonstrated that TD is associated with a three- to four-fold increased risk of diabetes mellitus, which is a known predictor of cardiovascular morbidity and mortality [Brand *et al.* 2014]. Current data suggest improvement in components of MetS with TRT, but large, placebo-controlled trials are lacking [Cunningham, 2015].

Chronic obstructive pulmonary disease and obstructive sleep apnea (OSA) have both been associated with TD with proposed mechanisms including hypercapnia, hypoxia, and in the case of OSA, sleep fragmentation-mediated dysregulation of diurnal hypothalamic rhythms that can improve with underlying disease treatment [Aasebo *et al.* 1993; Luboshitzky *et al.* 2002]. Chronic liver disease and/or alcoholism can alter hepatic SHBG production and affect the HPG axis centrally *via* hyperestrogenemia-mediated effects, whereas alcohol has additional, gonadotoxic effects [Bannister *et al.* 1987; Emanuele and Emanuele, 1998]. Hypothyroidism symptoms can mimic some symptoms of hypogonadism and should be considered as part of the evaluation despite ongoing controversy over normal thyroid-stimulating hormone (TSH) levels in older men [Boucai *et al.* 2011; Bremner *et al.* 2012]. Other medical conditions associated with TD in older men include acute illness, rheumatoid arthritis, chronic kidney disease, HIV with or without AIDS, hemochromatosis, and depression, all *via* multifactorial mechanisms [Kelly *et al.* 1984; Woolf *et al.* 1985; Kalyani *et al.* 2007; Khera *et al.* 2012]. TD has also been associated with erectile dysfunction (ED) and Peyronie's disease (PD), the latter of which is controversial [Nam *et al.* 2011; Cavallini *et al.* 2012; Isidori *et al.* 2014]. PD tends to occur in the same population as TD, and data have shown that TD leads to upregulation of transforming growth factor beta, resulting in corporal fibrosis [Traish and Guay, 2006], which can be reversed with TRT in animal models [Traish *et al.* 1999]. Yet, a recent, large, retrospective review found that men presenting with either PD or ED have a similar incidence of TD, suggesting the high rate of low testosterone in men with PD may be related more to the underlying sexual dysfunction [Kirby *et al.* 2015].

Several medications frequently prescribed in older men may also contribute to the development of TD. The frequently prescribed 5α-reductase inhibitors for prostate enlargement can induce mild hypogonadal symptoms [Thompson *et al.* 2003]. Many cancer treatments, such as alkylating agents, can significantly harm Leydig-cell function and spermatogenesis [Howell *et al.* 2001]. Systemic glucocorticoids have direct inhibitory effects on all levels of the HPG axis, which can persist up to 12 months after cessation of therapy [Morrison *et al.* 1994]. Similarly, any previous lifetime exposure to exogenous anabolic steroids or prior TRT can negatively impact the HPG axis for up to 2–3 years and even permanently in some cases [Jarow and Lipshultz, 1990; Coward *et al.* 2013]. Increasingly common, opioid analgesics can suppress the HPG axis centrally and peripherally, but the effects are short lived depending upon the half-life of agent used [Rajagopal *et al.* 2004; Katz and Mazer, 2009]. Commonly used antihypertensive (β-blockers) and anticholesterol (statins) medications can induce mild to moderate reductions in serum testosterone levels [Rosen *et al.* 1988; Schooling *et al.* 2013]. Whether the medication, underlying medical condition, or both are at fault is unclear, but TD and comorbid medical conditions, and associated treatments can lead to a self-reinforcing cycle and development of TD symptoms.

Diagnosis

The diagnosis of TD in aging men is based upon the presence of both clinical symptoms and low

serum testosterone levels similar to the approach used in younger or middle-aged men [Bhasin *et al.* 2010; Buvat *et al.* 2010], because high-quality, randomized trials are lacking in older men. Yet the diagnosis of TD in older men is more difficult due to the preponderance of symptoms associated with normal aging that overlap with those associated with TD. However, evaluating patients for biochemical TD alone can lead to significant over-diagnosis due to the clear age-related decrease in testosterone levels [Tajar *et al.* 2012]. In fact, many older men with 'low testosterone' are asymptomatic [Wu *et al.* 2010]. This dilemma has led many large medical societies and organizations to define the phenomenon of LOH as a 'clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels below those seen in young healthy males' [Wang *et al.* 2009]. For these reasons, defined etiologies of primary and secondary symptomatic hypogonadism must be differentiated from LOH during the initial evaluation; otherwise the apparent low testosterone may be a normal physiologic response with aging.

Clinical diagnosis

The majority of clinical symptoms associated with hypogonadism in aging men can be categorized as sexual or nonsexual. Sexual symptoms include decreased libido, decreased frequency of sexual thoughts, decreased frequency or rigidity of nocturnal erections, and ED [Morelli *et al.* 2007; Corona *et al.* 2014]. Nonsexual symptoms include fatigue, decreased energy, poor concentration, decreased sense of well-being, depressed mood, decreased vitality, and depression [Bhasin *et al.* 2010; Buvat *et al.* 2010]. Additional signs often associated with symptomatic hypogonadism include obesity, decreased muscle mass and strength, decreased bone-mineral density (BMD) and osteoporosis, hot flashes, and mild anemia [Dohle *et al.* 2012]. Physical examination is usually nonspecific but can reveal testicular atrophy or asymmetry, varicoceles, penile plaques or other abnormalities, decreased pubic hair, gynecomastia, visceral obesity, and diminished prostate volume, although some men with TD maintain an enlarged prostate [Corona *et al.* 2009]. Many of these signs and symptoms are nonspecific. Sexual symptoms, particularly decreased libido, have been shown to strongly correlate with serum testosterone levels [Travison *et al.* 2006; Corona *et al.* 2009]. Overall, the use of symptom questionnaires for screening or diagnosis is not encouraged due to poor specificity (30–40%), however the quantitative Androgen Deficiency in the Aging Male and the Aging Males' Symptoms questionnaires demonstrate higher sensitivities at 97% and 83%, respectively, and are utilized in some centers of excellence [Morley *et al.* 2006; Wang *et al.* 2009; Mohamed *et al.* 2010]. In addition, the ANDROTEST-structured interview is a useful clinical adjunct for screening in men with sexual dysfunction [Corona *et al.* 2006].

Laboratory diagnosis

In aging men who present with signs or symptoms of hypogonadism, the diagnosis must be confirmed with laboratory testing. Initial testing should include a total serum testosterone level drawn between 7 am and 11 am [Diver *et al.* 2003], due to diurnal variation. However, blunting of diurnal variation can occur in a significant proportion of older men [Crawford *et al.* 2007], and up to 30% of men with initially abnormal values will have normal levels on repeat testing [Brambilla *et al.* 2007]. As such, most experts agree that a second, confirmatory level should be obtained [Wang *et al.* 2009; Bhasin *et al.* 2010]. What constitutes a 'normal value' has not been clearly established in older men due to multiple issues including underlying physiologic complexity as previously discussed and inherent variations in laboratory testing. Laboratory techniques that provide good precision and accuracy are either radioimmunoassay or mass spectrometry, but their use is not standardized [Paduch *et al.* 2014]. Most laboratories and experts consider 10–12 nmol/l as the lower limit of normal based upon data from younger men [Wang *et al.* 2009; Bhasin *et al.* 2010; Buvat *et al.* 2010; Dohle *et al.* 2012]. However, some data suggest a more consistent manifestation of symptoms, and benefit from treatment, at levels below 6.4–8.0 nmol/l, particularly in older men [Wang *et al.* 2009; Yeap *et al.* 2012]. Recent data from the European Male Aging Study (EMAS) group correlating serum testosterone levels with 32 different hypogonadal symptoms in older men demonstrated different symptoms appear at different testosterone levels, but only with sexual symptoms (ED, low libido, and decreased nocturnal erections) was a continuous inverse relationship with serum testosterone levels statistically significant [Wu *et al.* 2010]. In addition, they found a five-fold and three-fold increased risk of death in men with severe TD and sexual dysfunction [Pye *et al.* 2014]. These

findings lead to the proposal of diagnostic criteria for symptomatic hypogonadism to include the presence of three sexual symptoms combined with a total testosterone level lower than 11 nmol/l or free testosterone lower than 220 pmol/l in those with equivocal total testosterone levels (8–11 nmol/l). Using these authors' strict criteria, only approximately 5% of men older than 70 years have hypogonadism, which is less than in other studies reporting up to 12% using less strict criteria [Araujo *et al.* 2004, 2007]. However, the EMAS group excluded men already diagnosed and treated, and their study population's mean body mass index (BMI) was 27 with a low rate of MetS likely not representative of the general population where rates of TD may be higher. It is known that older men often under report sexual symptoms due to embarrassment or misinterpretation as 'normal aging' [Baldwin *et al.* 2003]. Overall, in aging men, the exact total testosterone threshold below which symptoms ensue and treatment should initiate is unclear, and rigid thresholds should thus not be used [Wu *et al.* 2010]. Therefore, some experts recommend treatment for clearly symptomatic men even if serum testosterone levels are 'low-normal' and free testosterone levels are low [Morgentaler *et al.* 2014].

With such ambiguity in what constitutes 'normal', many clinicians will routinely determine free testosterone levels, with levels lower than 220–345 pmol/l considered abnormal. Equilibrium dialysis is the gold standard, but is expensive, complex, and commonly unavailable at most laboratories [Morgentaler *et al.* 2014; Lunenfeld *et al.* 2015]. An alternative is the Vermeulen calculation method, utilizing total testosterone, SHBG, and albumin levels [Vermeulen *et al.* 1999]. SHBG is particularly important to help interpret total testosterone levels in older men due to its variability based upon associated comorbidities. Some data demonstrate interindividual variation in androgen-receptor sensitivity due to cysteine adenine guanine (CAG) polymorphisms, explaining the presence of symptoms in the absence of 'low' testosterone levels [Rajender *et al.* 2007; Zitzmann, 2009]. Accordingly, some clinicians incorporate CAG evaluation in their diagnostic armamentarium [Morgentaler *et al.* 2014]. Serum gonadotropins (follicle-stimulating hormone and LH) are also helpful in distinguishing primary, secondary, and compensated hypogonadism, which can be difficult in older men with multiple comorbidities and medications that manipulate the HPG axis. Compensated hypogonadism is defined as low-normal testosterone (> 10 nmol/l), elevated LH (> 9.4 IU/l), and physical symptoms. It is common in older men and often progresses to more fulminant primary hypogonadism and need for treatment [Tajar *et al.* 2010]. In addition, serum prolactin, TSH, vitamin D, and estrogen levels are helpful in elucidating underlying etiologies, with the latter useful to calculate the testosterone:estrogen ratio [Bunch *et al.* 2002; Corona *et al.* 2007; McBride *et al.* 2015]. Assessment of other physical manifestations of hypogonadism, particularly in those with near castrate levels, should be considered, specifically, anemia and bone-density assessments, as these can improve with treatment [Snyder *et al.* 1999; Tajar *et al.* 2012; Hoppe *et al.* 2013; Spitzer *et al.* 2013].

Treatment

Benefits

TRT has the theoretical potential to improve many of the physiologic manifestations of deficiency. In general, the benefit of treatment for hypogonadism in older men is unclear due to lack of randomized controlled trials and other quality data. Sexual symptoms highly correlate with hypogonadism, yet data from interventional studies demonstrating improvement with treatment are unclear. Normal erections can occur in aging hypogonadal men, and increasing testosterone levels do not necessarily improve ED symptoms [Rhoden *et al.* 2002]. Likewise, mean serum testosterone levels in men with ED are often in the 'normal range' [Corona *et al.* 2004]. Two different meta-analyses agreed that TRT can improve libido, nocturnal erections, and sexual satisfaction, but the effect in older men is inconsistent and fades with time [Isidori *et al.* 2005; Bolona *et al.* 2007]. A more recent meta-analysis confirmed this but identified publication bias between industry-sponsored and unsponsored trials of TRT for LOH, explaining previously stated inconsistencies [Corona *et al.* 2014].

There is also a potential benefit of combining TRT with phosphodiesterase-5 inhibitors (PDE5Is) in hypogonadal men with ED symptoms. In hypogonadal men with symptoms of ED initially treated successfully with PDE5Is alone, further benefit by adding TRT has not been demonstrated [Spitzer *et al.* 2012]. However, in hypogonadal men with ED symptoms that do not experience satisfactory improvement with PDE5Is alone, TRT has been shown to 'salvage' these

men as PDE5I-treatment failures, particularly when serum testosterone levels are lower than 10 nmol/l [Buvat *et al.* 2011]. This was also confirmed in a recent meta-analysis [Corona *et al.* 2014]. Endocrine society guidelines [Bhasin *et al.* 2010] recommend offering TRT to men with low testosterone levels and low libido or ED, and in addition to PDE5I-treatment failures. In the context of the recent FDA statement, to support TRT in men with ED or low libido, clinicians should also identify an underlying etiology for symptomatic hypogonadism of which ED or low libido are a symptom.

Data associating age-related hypogonadism and risk for falls, reduced strength, muscle mass, physical performance, and frailty are available [Schaap *et al.* 2005; Krasnoff *et al.* 2010]. Some of these physical parameters, such as grip strength and muscle mass, can improve with TRT in healthy older men [Srinivas-Shankar *et al.* 2010; Hildreth *et al.* 2013]. However improvement in clinically significant physical function and performance-based measures in older men is less robust [Page *et al.* 2005; Storer *et al.* 2008; Srinivas-Shankar *et al.* 2010], and effects are often short lived [O'Connell *et al.* 2011]. Men with LOH are at risk for decreases in BMD and osteoporosis, and treatment may mitigate the risk. A few randomized studies mostly using injectable testosterone formulations have shown an improvement in lumbar and hip BMD, the latter of which is considered by some to reflect fracture risk [Amory *et al.* 2004; Aversa *et al.* 2012]. Yet a meta-analysis of quality studies only demonstrated improvements in lumber BMD [Tracz *et al.* 2006], and no studies to date have evaluated fracture risk. As mentioned, data demonstrating definitive improvement in obesity, diabetes, and/or MetS are not yet available, but several studies suggest improvements in obesity, waist circumference, insulin sensitivity, and diabetes parameters using various testosterone formulations [Heufelder *et al.* 2009; Cai *et al.* 2014; Hackett *et al.* 2014]. Conversely, other reports failed to demonstrate such findings [Jones *et al.* 2011; Gianatti *et al.* 2014; Traish, 2014]. Lastly, sparse data supporting improvements in depression [Giltay *et al.* 2010; Pope *et al.* 2010], and cognition [Azad *et al.* 2003; Cherrier *et al.* 2005], are suggestive of benefit but further research is needed.

Controversies and risk

TRT is generally considered a safe and effective treatment for TD in younger and middle-aged men, but the same may not be true for older hypogonadal men. Aging men inherently experience exaggerated treatment side effects due to reduced capacity to metabolize testosterone and higher burden of comorbid disease [Coviello *et al.* 2006]. Higher rates of erythrocytosis are seen in older men [Calof *et al.* 2005; Coviello *et al.* 2008], with some data suggesting the upper limit of safe levels may be lower in older men with various comorbidities [Gagnon *et al.* 1994; Danesh *et al.* 2000]. Men who desire to maintain their fertility should not be given exogenous testosterone without discussion of the negative effects on spermatogenesis and the inherent delay in recovery of spermatogenesis after treatment cessation, which in some cases is not spontaneous and may require additional medical treatment. In addition, any man with a history of breast cancer should not receive TRT, and all men undergoing treatment should be counseled regarding this rare but potential risk with long-term TRT [Medras *et al.* 2006].

Similarly, prostate cancer has historically been a contraindication to TRT with caution reflected in most guideline statements [Wang *et al.* 2009; Bhasin *et al.* 2010; Buvat *et al.* 2010; Dohle *et al.* 2012]. More recently, the 'saturation model' emerged [Morgentaler and Traish, 2009], establishing that prostate tissue, benign or malignant, is only sensitive to serum levels of testosterone below a certain threshold, above which prostate tissue behaves irrespective of androgen levels. Other data have confirmed these findings and propose a threshold level of approximately 8.6 mmol/l [Rastrelli *et al.* 2013]. Several studies also support the use of testosterone in men 'at risk' for prostate cancer without increasing their baseline odds of prostate cancer development [Roddam *et al.* 2008; Muller *et al.* 2012; Cui *et al.* 2014]. Yet the absence of large, long-term randomized controlled trials precludes a definitive answer and at-risk men should be appropriately screened for prostate cancer prior to initiation of, and at regular intervals, during treatment. A slight increase in prostate-specific antigen (PSA) can be expected with treatment initiation, particularly in severely hypogonadal males (< 8.6 mmol/l), which is usually modest (< 0.01 mmol/l) within the first 6 months of therapy [Bhasin *et al.* 2003]. Some clinical guidelines suggest waiting to check a serum PSA until after 6 months of treatment to allow for such physiologic changes [Dohle *et al.* 2012]. However, a PSA rise greater than 0.06 mmol/l within 18 months of therapy may indicate underlying, undiagnosed prostate cancer [Coward

et al. 2009]. In such cases, one should consider continuing TRT until underlying prostate cancer is confirmed because the many causes of hypogonadism, such as MetS, may have a greater mortality risk than prostate cancer that can potentially be mitigated by TRT.

In addition, a growing body of data demonstrates the safety of TRT in men with definitively treated, localized, low-to-intermediate risk (Gleason 6 or 7) prostate cancer biochemically free of recurrence 1–2 years after treatment with surgery [Kaufman and Graydon, 2004; Agarwal and Oefelein, 2005; Khera *et al.* 2009; Pastuszak *et al.* 2013a], or radiation [Morales *et al.* 2009; Pastuszak *et al.* 2013b; Balbontin *et al.* 2014]. Likewise, limited reports of testosterone use in hypogonadal men on active surveillance protocols appear promising [Morales, 2011; Morgentaler *et al.* 2011]. Yet one must emphasize the data for TRT in men with a history of prostate cancer are without randomized or placebo controlled trials and should be interpreted with caution. Historically a contraindication to treatment, TRT use in the setting of benign prostatic hyperplasia (BPH) is now considered safe with no data demonstrating exacerbation of symptoms with treatment [Calof *et al.* 2005], and in fact some suggesting improvement in lower urinary tract symptoms for those with LOH and BPH [Shigehara *et al.* 2011; Yassin *et al.* 2014].

More controversial is the relationship between TRT, CVD, and mortality. Historically, low serum testosterone levels have been associated with increases in several known risk factors for CVD including C-reactive protein, carotid intima media thickness, interleukin-1β, BMI, blood pressure, lipid levels, and coagulation profiles [Muller *et al.* 2004; Nettleship *et al.* 2007; Aversa *et al.* 2010; Kaplan *et al.* 2010]. Likewise several large population-based and observational studies have established an inverse relationship between serum testosterone levels and risk of developing CVD and CVD-related or diabetes-related mortality [Khaw *et al.* 2007; Corona *et al.* 2010; Ohlsson *et al.* 2011; Haring *et al.* 2013; Muraleedharan *et al.* 2013]. A few meta-analyses have shown no increase in cardiovascular adverse effects or mortality with TRT [Calof *et al.* 2005; Fernandez-Balsells *et al.* 2010; Carson and Rosano, 2012]. In addition, recent, large retrospective studies have suggested TRT in aging hypogonadal men can improve overall mortality [Shores *et al.* 2012; Muraleedharan *et al.* 2013]. Yet to date there are no randomized trials or other high-quality data to validate these findings. In fact, more recently, a handful of studies assert potentially worse cardiovascular events and mortality in older hypogonadal men on TRT [Basaria *et al.* 2010; Vigen *et al.* 2013; Xu *et al.* 2013; Finkle *et al.* 2014]. These data contain several design flaws and questionable statistics, leading to well-publicized controversy [Morgentaler *et al.* 2015; Sigman, 2015].

Nonetheless, the FDA reviewed the current data on TRT in men with LOH in March 2015 and determined that the benefit and safety of testosterone use in these men have not been established, and required amending manufacturer labels to reflect the possibility of increased risk for heart attack or stroke with treatment. Their conclusion statement regarding CVD is the 'signal of cardiovascular risk is weak and only a prospective, well-controlled clinical trial could determine whether testosterone causes cardiovascular harm'. Moreover, the FDA report states: 'The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone', which the FDA recommended be added to manufacturer labels for testosterone products. Lastly, the statement indicated that exogenous testosterone should not be used for hypogonadism without a 'defined cause' considered to be a 'disorder of the testicles, pituitary gland, or brain resulting in hypogonadism'. Since the FDA statement, the American Association of Clinical Endocrinologists (AACE) released a position statement acknowledging the 'weak signal' for cardiovascular risk with TRT and stated that 'there is no compelling evidence that testosterone therapy either increases or decreases cardiovascular risk' [Goodman *et al.* 2015]. Furthermore, the AACE statement indicates that 'men with unequivocally low total and/or free testosterone after thorough diagnostic workup should be considered for TRT and extra caution should be exercised in the frail elderly'. Bolstering the AACE recommendations is a very recent, retrospective review of over 80,000 veterans demonstrating a statistically significant reduction in all-cause mortality, myocardial infarction and stroke in those with normalization of total testosterone levels with TRT [Sharma *et al.* 2015]. Ultimately, in the context of the FDA statement, the distinction of exactly which 'disorders' result in dysfunction of the testicles, pituitary gland, or brain to the clinician. The

future burden will be on clinicians to clearly identify and document any and all medical conditions that physiologically explain a patient's symptomatic primary, secondary, or mixed hypogonadism to justify treatment.

Conclusion

As testosterone use continues to rise along with the increased recognition and prevalence of hypogonadism in the aging male population, the temptation for treatment with TRT in older men will continue to persist for providers and patients alike. It is important that clinicians understand the complex, underlying physiology and strong association with many chronic medical conditions and medications in order to appreciate fully the difficulty in diagnosis. Even in older men who meet diagnostic criteria for LOH, the benefit of treatment in this setting alone is not clear and may be associated with negative impacts on cardiovascular health or mortality. To the contrary, for men with identifiable etiologies or primary or secondary hypogonadism, treatment may be warranted regardless of age.

The authors encourage clinicians to only offer TRT to men diagnosed with symptomatic hypogonadism based upon a careful history demonstrating clear symptoms along with convincing laboratory data, and only after a thorough discussion of the uncertain benefits and possible risks of treatment. Informing patients of the recent FDA statement regarding TRT in aging men is of utmost importance in the current healthcare climate, particularly because testosterone use for this population may now be considered 'off-label'. With these caveats, the authors also want to reiterate the vast literature of known and proven benefits of testosterone normalization, which must also be carefully considered during the decision of whether or not to offer treatment. The best approach to TRT for the population of older hypogonadal men is probably one of full disclosure and shared decision-making.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Aasebo, U., Gyltnes, A., Bremnes, R., Aakvaag, A. and Slordal, L. (1993) Reversal of sexual impotence in male patients with chronic obstructive pulmonary disease and hypoxemia with long-term oxygen therapy. *J Steroid Biochem Mol Biol* 46: 799–803.

Agarwal, P. and Oefelein, M. (2005) Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 173: 533–536.

Amory, J., Watts, N., Easley, K., Sutton, P., Anawalt, B., Matsumoto, A. *et al.* (2004) Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 89: 503–510.

Araujo, A., Esche, G., Kupelian, V., O'Donnell, A., Travison, T., Williams, R. *et al.* (2007) Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 92: 4241–4247.

Araujo, A., O'Donnell, A., Brambilla, D., Simpson, W., Longcope, C., Matsumoto, A. *et al.* (2004) Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 89: 5920–5926.

Aversa, A., Bruzziches, R., Francomano, D., Greco, E., Fornari, R., Di Luigi, L. *et al.* (2012) Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. *Aging Male* 15: 96–102.

Aversa, A., Bruzziches, R., Francomano, D., Spera, G. and Lenzi, A. (2010) Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 33: 776–783.

Azad, N., Pitale, S., Barnes, W. and Friedman, N. (2003) Testosterone treatment enhances regional brain perfusion in hypogonadal men. *J Clin Endocrinol Metab* 88: 3064–3068.

Balbontin, F., Moreno, S., Bley, E., Chacon, R., Silva, A. and Morgentaler, A. (2014) Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. *BJU Int* 114: 125–130.

Baldwin, K., Ginsberg, P. and Harkaway, R. (2003) Under-reporting of erectile dysfunction among men with unrelated urologic conditions. *Int J Impot Res* 15: 87–89.

Bannister, P., Oakes, J., Sheridan, P. and Losowsky, M. (1987) Sex hormone changes in chronic liver disease: a matched study of alcoholic *versus* non-alcoholic liver disease. *Q J Med* 63: 305–313.

Basaria, S., Coviello, A., Travison, T., Storer, T., Farwell, W., Jette, A. *et al.* (2010) Adverse events

associated with testosterone administration. *N Engl J Med* 363: 109–122.

Bhasin, S., Cunningham, G., Hayes, F., Matsumoto, A., Snyder, P., Swerdloff, R. *et al.* (2010) Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 95: 2536–2559.

Bhasin, S., Singh, A., Mac, R., Carter, B., Lee, M. and Cunningham, G. (2003) Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J Androl* 24: 299–311.

Bolona, E., Uraga, M., Haddad, R., Tracz, M., Sideras, K., Kennedy, C. *et al.* (2007) Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 82: 20–28.

Bornstein, S., Rutkowski, H. and Vrezas, I. (2004) Cytokines and steroidogenesis. *Mol Cell Endocrinol* 215: 135–141.

Boucai, L., Hollowell, J. and Surks, M. (2011) An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. *Thyroid* 21: 5–11.

Brambilla, D., O'Donnell, A., Matsumoto, A. and McKinlay, J. (2007) Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf)* 67: 853–862.

Brand, J., Rovers, M., Yeap, B., Schneider, H., Tuomainen, T., Haring, R. *et al.* (2014) Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. *PLoS One* 9: e100409.

Bremner, A., Feddema, P., Leedman, P., Brown, S., Beilby, J., Lim, E. *et al.* (2012) Age-related changes in thyroid function: a longitudinal study of a community-based cohort. *J Clin Endocrinol Metab* 97: 1554–1562.

Bremner, W., Vitiello, M. and Prinz, P. (1983) Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 56: 1278–1281.

Bunch, T., Abraham, D., Wang, S. and Meikle, A. (2002) Pituitary radiographic abnormalities and clinical correlates of hypogonadism in elderly males presenting with erectile dysfunction. *Aging Male* 5: 38–46.

Buvat, J., Maggi, M., Gooren, L., Guay, A., Kaufman, J., Morgentaler, A. *et al.* (2010) Endocrine aspects of male sexual dysfunctions. *J Sex Med* 7: 1627–1656.

Buvat, J., Montorsi, F., Maggi, M., Porst, H., Kaipia, A., Colson, M. *et al.* (2011) Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 8: 284–293.

Cai, X., Tian, Y., Wu, T., Cao, C., Li, H. and Wang, K. (2014) Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Asian J Androl* 16: 146–152.

Calof, O., Singh, A., Lee, M., Kenny, A., Urban, R., Tenover, J. *et al.* (2005) Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 60: 1451–1457.

Canales, B., Zapzalka, D., Ercole, C., Carey, P., Haus, E., Aeppli, D. *et al.* (2005) Prevalence and effect of varicoceles in an elderly population. *Urology* 66: 627–631.

Carson, C., 3rd and Rosano, G. (2012) Exogenous testosterone, cardiovascular events, and cardiovascular risk factors in elderly men: a review of trial data. *J Sex Med* 9: 54–67.

Cavallini, G., Biagiotti, G. and Lo Giudice, C. (2012) Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 33: 381–388.

Cherrier, M., Matsumoto, A., Amory, J., Asthana, S., Bremner, W., Peskind, E. *et al.* (2005) Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 64: 2063–2068.

Corona, G., Isidori, A., Buvat, J., Aversa, A., Rastrelli, G., Hackett, G. *et al.* (2014) Testosterone supplementation and sexual function: a meta-analysis study. *J Sex Med* 11: 1577–1592.

Corona, G., Mannucci, E., Fisher, A., Lotti, F., Ricca, V., Balercia, G. *et al.* (2007) Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. *J Sex Med* 4: 1485–1493.

Corona, G., Mannucci, E., Mansani, R., Petrone, L., Bartolini, M., Giommi, R. *et al.* (2004) Aging and pathogenesis of erectile dysfunction. *Int J Impot Res* 16: 395–402.

Corona, G., Mannucci, E., Petrone, L., Balercia, G., Fisher, A., Chiarini, V. *et al.* (2006) Androtest: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. *J Sex Med* 3: 706–715.

Corona, G., Mannucci, E., Ricca, V., Lotti, F., Boddi, V., Bandini, E. *et al.* (2009) The age-related decline of testosterone is associated with different

specific symptoms and signs in patients with sexual dysfunction. *Int J Androl* 32: 720–728.

Corona, G., Monami, M., Boddi, V., Cameron-Smith, M., Fisher, A., De Vita, G. *et al.* (2010) Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. *J Sex Med* 7: 1557–1564.

Coviello, A., Kaplan, B., Lakshman, K., Chen, T., Singh, A. and Bhasin, S. (2008) Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 93: 914–919.

Coviello, A., Lakshman, K., Mazer, N. and Bhasin, S. (2006) Differences in the apparent metabolic clearance rate of testosterone in young and older men with gonadotropin suppression receiving graded doses of testosterone. *J Clin Endocrinol Metab* 91: 4669–4675.

Coward, R., Rajanahally, S., Kovac, J., Smith, R., Pastuszak, A. and Lipshultz, L. (2013) Anabolic steroid induced hypogonadism in young men. *J Urol* 190: 2200–2205.

Coward, R., Simhan, J. and Carson, C., 3rd (2009) Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. *BJU Int* 103: 1179–1183.

Crawford, E., Barqawi, A., O'Donnell, C. and Morgentaler, A. (2007) The association of time of day and serum testosterone concentration in a large screening population. *BJU Int* 100: 509–513.

Cui, Y., Zong, H., Yan, H. and Zhang, Y. (2014) The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 17: 132–143.

Cunningham, G. (2015) Testosterone and metabolic syndrome. *Asian J Androl* 17: 192–196.

Danesh, J., Collins, R., Peto, R. and Lowe, G. (2000) Haematocrit, viscosity, erythrocyte sedimentation rate: meta-analyses of prospective studies of coronary heart disease. *Eur Heart J* 21: 515–520.

Diver, M., Imtiaz, K., Ahmad, A., Vora, J. and Fraser, W. (2003) Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. *Clin Endocrinol (Oxf)* 58: 710–717.

Dohle, G., Arver, S., Bettocchi, C., Jones, T., Kliesch, S. and Punab, M. (2012) *Guidelines on Male Hypogonadism*. Arnhem: European Association of Urology.

Emanuele, M. and Emanuele, N. (1998) Alcohol's effects on male reproduction. *Alcohol Health Res World* 22: 195–201.

Fernandez-Balsells, M., Murad, M., Lane, M., Lampropulos, J., Albuquerque, F., Mullan, R. *et al.* (2010) Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 95: 2560–2575.

Finkle, W., Greenland, S., Ridgeway, G., Adams, J., Frasco, M., Cook, M. *et al.* (2014) Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 9: e85805.

Gagnon, D., Zhang, T., Brand, F. and Kannel, W. (1994) Hematocrit and the risk of cardiovascular disease – the Framingham study: a 34-year follow-up. *Am Heart J* 127: 674–682.

Gianatti, E., Dupuis, P., Hoermann, R., Strauss, B., Wentworth, J., Zajac, J. *et al.* (2014) Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 37: 2098–2107.

Giltay, E., Tishova, Y., Mskhalaya, G., Gooren, L., Saad, F. and Kalinchenko, S. (2010) Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med* 7: 2572–2582.

Goodman, N., Guay, A., Dandona, P., Dhindsa, S., Faiman, C., Cunningham, G. *et al.* (2015) American Association of Clinical Endocrinologist and American College of Endocrinology Position Statement on the Association of Teststerone and Cardiovascular Risk. *Endocr Pract* 21: 1066–1073.

Hackett, G., Cole, N., Bhartia, M., Kennedy, D., Raju, J. and Wilkinson, P. (2014) Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the blast study. *J Sex Med* 11: 840–856.

Handelsman, D. (2013) Global trends in testosterone prescribing, 2000–2011: expanding the spectrum of prescription drug misuse. *Med J Aust* 199: 548–551.

Haring, R., Teng, Z., Xanthakis, V., Coviello, A., Sullivan, L., Bhasin, S. *et al.* (2013) Association of sex steroids, gonadotrophins, and their trajectories with clinical cardiovascular disease and all-cause mortality in elderly men from the Framingham Heart Study. *Clin Endocrinol (Oxf)* 78: 629–634.

Harman, S., Metter, E., Tobin, J., Pearson, J. and Blackman, M. (2001) Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 86: 724–731.

Hautanen, A. (2000) Synthesis and regulation of sex hormone-binding globulin in obesity. *Int J Obes Relat Metab Disord* 24(Suppl. 2): S64–S70.

Hayes, F., Decruz, S., Seminara, S., Boepple, P. and Crowley, W., Jr (2001) Differential regulation of gonadotropin secretion by testosterone in the

human male: absence of a negative feedback effect of testosterone on follicle-stimulating hormone secretion. *J Clin Endocrinol Metab* 86: 53–58.

Heufelder, A., Saad, F., Bunck, M. and Gooren, L. (2009) Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 30: 726–733.

Hildreth, K., Barry, D., Moreau, K., Vande Griend, J., Meacham, R., Nakamura, T. *et al.* (2013) Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab* 98: 1891–1900.

Hoppe, E., Bouvard, B., Royer, M., Chappard, D., Audran, M. and Legrand, E. (2013) Is androgen therapy indicated in men with osteoporosis? *Joint Bone Spine* 80: 459–465.

Howell, S., Radford, J., Adams, J., Smets, E., Warburton, R. and Shalet, S. (2001) Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. *Clin Endocrinol (Oxf)* 55: 315–324.

Isidori, A., Buvat, J., Corona, G., Goldstein, I., Jannini, E., Lenzi, A. *et al.* (2014) A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment – a systematic review. *Eur Urol* 65: 99–112.

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

Isidori, A., Giannetta, E., Gianfrilli, D., Greco, E., Bonifacio, V., Aversa, A. *et al.* (2005) Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 63: 381–394.

Jarow, J., Chen, H., Rosner, T., Trentacoste, S. and Zirkin, B. (2001) Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. *J Androl* 22: 640–645.

Jarow, J. and Lipshultz, L. (1990) Anabolic steroid-induced hypogonadotropic hypogonadism. *Am J Sports Med* 18: 429–431.

Jones, T., Arver, S., Behre, H., Buvat, J., Meuleman, E., Moncada, I. *et al.* (2011) Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 34: 828–837.

Kalyani, R., Gavini, S. and Dobs, A. (2007) Male hypogonadism in systemic disease. *Endocrinol Metab Clin North Am* 36: 333–348.

Kaplan, S., Johnson-Levonas, A., Lin, J., Shah, A. and Meehan, A. (2010) Elevated high sensitivity C-reactive protein levels in aging men with low testosterone. *Aging Male* 13: 108–112.

Katz, N. and Mazer, N. (2009) The impact of opioids on the endocrine system. *Clin J Pain* 25: 170–175.

Kaufman, J. and Graydon, R. (2004) Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 172: 920–922.

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

Kelly, T., Edwards, C., Meikle, A. and Kushner, J. (1984) Hypogonadism in hemochromatosis: reversal with iron depletion. *Ann Intern Med* 101: 629–632.

Khaw, K., Dowsett, M., Folkerd, E., Bingham, S., Wareham, N., Luben, R. *et al.* (2007) 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* 116: 2694–2701.

Khera, M., Bhattacharya, R., Blick, G., Kushner, H., Nguyen, D. and Miner, M. (2012) The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). *Aging Male* 15: 14–21.

Khera, M., Grober, E., Najari, B., Colen, J., Mohamed, O., Lamb, D. *et al.* (2009) Testosterone replacement therapy following radical prostatectomy. *J Sex Med* 6: 1165–1170.

Kirby, E., Verges, D., Matthews, J., Carson, C. and Coward, R. (2015) Low testosterone has a similar prevalence among men with sexual dysfunction due to either Peyronie's disease or erectile dysfunction and does not correlate with Peyronie's disease severity. *J Sex Med* 12: 690–696.

Krasnoff, J., Basaria, S., Pencina, M., Jasuja, G., Vasan, R., Ulloor, J. *et al.* (2010) Free testosterone levels are associated with mobility limitation and physical performance in community-dwelling men: the Framingham Offspring Study. *J Clin Endocrinol Metab* 95: 2790–2799.

Luboshitzky, R., Aviv, A., Hefetz, A., Herer, P., Shen-Orr, Z., Lavie, L. *et al.* (2002) Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. *J Clin Endocrinol Metab* 87: 3394–3398.

Lunenfeld, B., Mskhalaya, G., Zitzmann, M., Arver, S., Kalinchenko, S., Tishova, Y. *et al.* (2015) Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male* 18: 5–15.

Maggio, M., Lauretani, F., Ceda, G., Bandinelli, S., Basaria, S., Paolisso, G. *et al.* (2010) Estradiol and metabolic syndrome in older Italian men: the InCHIANTI Study. *J Androl* 31: 155–162.

Manni, A., Pardridge, W., Cefalu, W., Nisula, B., Bardin, C., Santner, S. *et al.* (1985) Bioavailability of albumin-bound testosterone. *J Clin Endocrinol Metab* 61: 705–710.

McBride, J., Carson, C. and Coward, R. (2015) Diagnosis and management of testosterone deficiency. *Asian J Androl* 17: 177–186.

McGill, J., Shoskes, D. and Sabanegh, E. (2012) Androgen deficiency in older men: indications, advantages, and pitfalls of testosterone replacement therapy. *Cleve Clin J Med* 79: 797–806.

Medras, M., Filus, A., Jozkow, P., Winowski, J. and Sicinska-Werner, T. (2006) Breast cancer and long-term hormonal treatment of male hypogonadism. *Breast Cancer Res Treat* 96: 263–265.

Mohamed, O., Freundlich, R., Dakik, H., Grober, E., Najari, B., Lipshultz, L. *et al.* (2010) The quantitative ADAM questionnaire: a new tool in quantifying the severity of hypogonadism. *Int J Impot Res* 22: 20–24.

Morales, A. (2011) Effect of testosterone administration to men with prostate cancer is unpredictable: a word of caution and suggestions for a registry. *BJU Int* 107: 1369–1373.

Morales, A., Black, A. and Emerson, L. (2009) Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int* 103: 62–64.

Morelli, A., Corona, G., Filippi, S., Ambrosini, S., Forti, G., Vignozzi, L. *et al.* (2007) Which patients with sexual dysfunction are suitable for testosterone replacement therapy? *J Endocrinol Invest* 30: 880–888.

Morgentaler, A., Feibus, A. and Baum, N. (2015) Testosterone and cardiovascular disease – the controversy and the facts. *Postgrad Med* 127: 159–165.

Morgentaler, A., Khera, M., Maggi, M. and Zitzmann, M. (2014) Commentary: who is a candidate for testosterone therapy? A synthesis of international expert opinions. *J Sex Med* 11: 1636–1645.

Morgentaler, A., Lipshultz, L., Bennett, R., Sweeney, M., Avila, D., Jr and Khera, M. (2011) Testosterone therapy in men with untreated prostate cancer. *J Urol* 185: 1256–1260.

Morgentaler, A. and Traish, A. (2009) Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol* 55: 310–320.

Morley, J., Perry, H., 3rd, Kevorkian, R. and Patrick, P. (2006) Comparison of screening questionnaires for the diagnosis of hypogonadism. *Maturitas* 53: 424–429.

Morrison, D., Capewell, S., Reynolds, S., Thomas, J., Ali, N., Read, G. *et al.* (1994) Testosterone levels during systemic and inhaled corticosteroid therapy. *Respir Med* 88: 659–663.

Muller, M., Van Den Beld, A., Bots, M., Grobbee, D., Lamberts, S. and Van Der Schouw, Y. (2004) Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation* 109: 2074–2079.

Muller, R., Gerber, L., Moreira, D., Andriole, G., Castro-Santamaria, R. and Freedland, S. (2012) Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. *Eur Urol* 62: 757–764.

Muraleedharan, V., Marsh, H., Kapoor, D., Channer, K. and Jones, T. (2013) Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 169: 725–733.

Nam, H., Park, H. and Park, N. (2011) Does testosterone deficiency exaggerate the clinical symptoms of Peyronie's disease? *Int J Urol* 18: 796–800.

Nettleship, J., Pugh, P., Channer, K., Jones, T. and Jones, R. (2007) Inverse relationship between serum levels of interleukin-1beta and testosterone in men with stable coronary artery disease. *Horm Metab Res* 39: 366–371.

O'Connell, M., Roberts, S., Srinivas-Shankar, U., Tajar, A., Connolly, M., Adams, J. *et al.* (2011) Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? *J Clin Endocrinol Metab* 96: 454–458.

Ohlsson, C., Barrett-Connor, E., Bhasin, S., Orwoll, E., Labrie, F., Karlsson, M. *et al.* (2011) High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. *J Am Coll Cardiol* 58: 1674–1681.

Paduch, D., Brannigan, R., Fuchs, E., Kim, E., Marmar, J. and Sandlow, J. (2014) The laboratory diagnosis of testosterone deficiency. *Urology* 83: 980–988.

Page, S., Amory, J., Bowman, F., Anawalt, B., Matsumoto, A., Bremner, W. *et al.* (2005) Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 90: 1502–1510.

Pastuszak, A., Pearlman, A., Godoy, G., Miles, B., Lipshultz, L. and Khera, M. (2013b) Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *Int J Impot Res* 25: 24–28.

Pastuszak, A., Pearlman, A., Lai, W., Godoy, G., Sathyamoorthy, K., Liu, J. *et al.* (2013a) Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol* 190: 639–644.

Pope, H., Jr, Amiaz, R., Brennan, B., Orr, G., Weiser, M., Kelly, J. *et al.* (2010) Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J Clin Psychopharmacol* 30: 126–134.

Pye, S., Huhtaniemi, I., Finn, J., Lee, D., O'Neill, T., Tajar, A. *et al.* (2014) Late-onset hypogonadism and mortality in aging men. *J Clin Endocrinol Metab* 99: 1357–1366.

Rajagopal, A., Vassilopoulou-Sellin, R., Palmer, J., Kaur, G. and Bruera, E. (2004) Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer* 100: 851–858.

Rajender, S., Singh, L. and Thangaraj, K. (2007) Phenotypic heterogeneity of mutations in androgen receptor gene. *Asian J Androl* 9: 147–179.

Rastrelli, G., Corona, G., Vignozzi, L., Maseroli, E., Silverii, A., Monami, M. *et al.* (2013) Serum PSA as a predictor of testosterone deficiency. *J Sex Med* 10: 2518–2528.

Rhoden, E., Teloken, C., Sogari, P. and Souto, C. (2002) The relationship of serum testosterone to erectile function in normal aging men. *J Urol* 167: 1745–1748.

Roddam, A., Allen, N., Appleby, P. and Key, T. (2008) Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 100: 170–183.

Rosen, R., Kostis, J. and Jekelis, A. (1988) Beta-blocker effects on sexual function in normal males. *Arch Sex Behav* 17: 241–255.

Rosner, W. (1991) Plasma steroid-binding proteins. *Endocrinol Metab Clin North Am* 20: 697–720.

Schaap, L., Pluijm, S., Smit, J., Van Schoor, N., Visser, M., Gooren, L. *et al.* (2005) The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. *Clin Endocrinol (Oxf)* 63: 152–160.

Schooling, C., Au Yeung, S., Freeman, G. and Cowling, B. (2013) The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med* 11: 57.

Sharma, R., Oni, O., Gupta, K., Chen, G., Sharma, M., Dawn, B. *et al.* (2015) Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J* 36: 2706–2715.

Shigehara, K., Sugimoto, K., Konaka, H., Iijima, M., Fukushima, M., Maeda, Y. *et al.* (2011) Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. *Aging Male* 14: 53–58.

Shores, M., Smith, N., Forsberg, C., Anawalt, B. and Matsumoto, A. (2012) Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 97: 2050–2058.

Sigman, M. (2015) Testosterone therapy: many players and much controversy. *Fertil Steril* 103: 1144–1145.

Smith, R., Coward, R., Kovac, J. and Lipshultz, L. (2013) The evidence for seasonal variations of testosterone in men. *Maturitas* 74: 208–212.

Snyder, P., Peachey, H., Hannoush, P., Berlin, J., Loh, L., Holmes, J. *et al.* (1999) Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 84: 1966–1972.

Spitzer, M., Basaria, S., Travison, T., Davda, M., Paley, A., Cohen, B. *et al.* (2012) Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med* 157: 681–691.

Spitzer, M., Huang, G., Basaria, S., Travison, T. and Bhasin, S. (2013) Risks and benefits of testosterone therapy in older men. *Nat Rev Endocrinol* 9: 414–424.

Srinivas-Shankar, U., Roberts, S., Connolly, M., O'Connell, M., Adams, J., Oldham, J. *et al.* (2010) Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 95: 639–650.

Storer, T., Woodhouse, L., Magliano, L., Singh, A., Dzekov, C., Dzekov, J. *et al.* (2008) Changes in muscle mass, muscle strength, and power but not physical function are related to testosterone dose in healthy older men. *J Am Geriatr Soc* 56: 1991–1999.

Tajar, A., Forti, G., O'Neill, T., Lee, D., Silman, A., Finn, J. *et al.* (2010) Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab* 95: 1810–1818.

Tajar, A., Huhtaniemi, I., O'Neill, T., Finn, J., Pye, S., Lee, D. *et al.* (2012) Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *J Clin Endocrinol Metab* 97: 1508–1516.

Tanrikut, C., Goldstein, M., Rosoff, J., Lee, R., Nelson, C. and Mulhall, J. (2011) Varicocele as a risk factor for androgen deficiency and effect of repair. *BJU Int* 108: 1480–1484.

Thompson, I., Goodman, P., Tangen, C., Lucia, M., Miller, G., Ford, L. *et al.* (2003) The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349: 215–224.

Tracz, M., Sideras, K., Bolona, E., Haddad, R., Kennedy, C., Uraga, M. *et al.* (2006) Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab* 91: 2011–2016.

Traish, A. (2014) Testosterone and weight loss: the evidence. *Curr Opin Endocrinol Diabetes Obes* 21: 313–322.

Traish, A. and Guay, A. (2006) Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med* 3: 382–387.

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

Traish, A., Saad, F., Feeley, R. and Guay, A. (2009a) The dark side of testosterone deficiency: III. Cardiovascular disease. *J Androl* 30: 477–494.

Traish, A., Saad, F. and Guay, A. (2009b) The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. *J Androl* 30: 23–32.

Travison, T., Morley, J., Araujo, A., O'Donnell, A. and McKinlay, J. (2006) The relationship between libido and testosterone levels in aging men. *J Clin Endocrinol Metab* 91: 2509–2513.

Vermeulen, A. and Kaufman, J. (1995) Ageing of the hypothalamo-pituitary-testicular axis in men. *Horm Res* 43: 25–28.

Vermeulen, A., Kaufman, J., Deslypere, J. and Thomas, G. (1993) Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab* 76: 1140–1146.

Vermeulen, A., Kaufman, J. and Giagulli, V. (1996) Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. *J Clin Endocrinol Metab* 81: 1821–1826.

Vermeulen, A., Verdonck, L. and Kaufman, J. (1999) A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 84: 3666–3672.

Vigen, R., O'Donnell, C., Baron, A., Grunwald, G., Maddox, T., Bradley, S. *et al.* (2013) Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 310: 1829–1836.

Wang, C., Nieschlag, E., Swerdloff, R., Behre, H., Hellstrom, W., Gooren, L. *et al.* (2009) Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *J Androl* 30: 1–9.

Woolf, P., Hamill, R., McDonald, J., Lee, L. and Kelly, M. (1985) Transient hypogonadotropic hypogonadism caused by critical illness. *J Clin Endocrinol Metab* 60: 444–450.

Wu, F., Tajar, A., Beynon, J., Pye, S., Silman, A., Finn, J. *et al.* (2010) Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 363: 123–135.

Wu, F., Tajar, A., Pye, S., Silman, A., Finn, J., O'Neill, T. *et al.* (2008) Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab* 93: 2737–2745.

Xu, L., Freeman, G., Cowling, B. and Schooling, C. (2013) Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 11: 108.

Yassin, D., El Douaihy, Y., Yassin, A., Kashanian, J., Shabsigh, R. and Hammerer, P. (2014) Lower urinary tract symptoms improve with testosterone replacement therapy in men with late-onset hypogonadism: 5-year prospective, observational and longitudinal registry study. *World J Urol* 32: 1049–1054.

Yeap, B., Alfonso, H., Chubb, S., Handelsman, D., Hankey, G., Norman, P. *et al.* (2012) Reference ranges and determinants of testosterone, dihydrotestosterone, and estradiol levels measured using liquid chromatography-tandem mass spectrometry in a population-based cohort of oder men. *J Clin Endocrinol Metab* 97: 4030–4039.

Zarotsky, V., Huang, M., Carman, W., Morgentaler, A., Singhal, P., Coffin, D. *et al.* (2014) Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology* 2: 819–834.

Zitzmann, M. (2009) The role of the CAG repeat androgen receptor polymorphism in andrology. *Front Horm Res* 37: 52–61.