Testosterone deficiency syndrome: benefits, risks, and realities associated with testosterone replacement therapy

Jacob Hassan, MD,[1] Jack Barkin, MD[2]

[1]Division of Urology, Credit Valley Hospital, Trillium Health Partners, Mississauga, Ontario, Canada

[2]Department of Surgery, University of Toronto, Toronto, Ontario, Canada

HASSAN J, BARKIN J. Testosterone deficiency syndrome: benefits, risks, and realities associated with testosterone replacement therapy. *Can J Urol* 2016;23(Suppl 1):20-30.

Testosterone deficiency syndrome, which has sometimes been termed age-related or late-onset hypogonadism, is a syndrome characterized by both clinical manifestations as well as a biochemical deficiency of testosterone. This condition is associated with considerable morbidity and mortality, accounting for billions of dollars in health care costs. There is some evidence that suggests that restoring testosterone levels in these individuals may help to manage or delay progression of the associated morbidities. Furthermore, despite controversies in the literature and media, testosterone replacement has proven to be quite safe in most men with minimal if any adverse effects when dosing to achieve the eugonadal range. It is nevertheless very important for clinicians to be aware of the possible risks and contraindications of treatment to ensure proper patient selection and appropriate monitoring.

Key Words: testosterone deficiency syndrome, hypogonadism, testosterone replacement therapy

Introduction

Male hypogonadism is a clinical syndrome caused by androgen deficiency, which may adversely affect multiple organ functions and quality of life. It is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis and can be broadly classified, based on the level of disturbance, as either primary (testicular failure: biochemically associated with high gonadotropins- follicle-stimulating hormone (FSH) and luteinizing hormone (LH)), secondary (hypothalamic and/or pituitary failure: low FSH and LH, or mixed (combination of primary and secondary). Testosterone deficiency syndrome as it is termed in the recent Canadian Clinical Practice Guidelines[1] is often age-related hypogonadism where testosterone levels are low, but the normal physiologic feedback pathway has been lost as demonstrated by the fact that FSH and LH levels are not elevated.

There are various clinical manifestations of hypogonadism, as shown in Table 1. While these signs and symptoms are characteristic of hypogonadal men, they are by no means specific, and thus biochemical parameters are necessary to establish a diagnosis.

It has been estimated that the crude Canadian prevalence of biochemical testosterone deficiency is 25% among men aged 40 to 62 years.[2] A larger US-based biochemical prevalence study, the Hypogonadism in Males (HIM) study, estimated that 39% of men aged 45 and above are testosterone deficient based on a total testosterone cut off of 300 ng/dL.[3] Far fewer men, however, are symptomatic and thus they are not

Address correspondence to Dr. Jacob Hassan, Credit Valley Hospital, Trillium Health Partners, 2200 Eglinton Avenue West , Mississauga, ON L5M 2N1 Canada

TABLE 1. **Signs and symptoms of hypogonadism**

Physical signs of hypogonadism

- Change in body composition with more central body fat
- Gynecomastia
- Testicular atrophy
- Muscular atrophy
- Osteoporotic fracture
- Loss of height
- Loss of facial, axillary and pubic hair

Symptoms of hypogonadism

- Mood changes
- Sleep disturbances
- Reduced libido
- Decreased energy
- Fatigue
- Decreased muscle strength
- Muscle aches
- Hot flashes
- Decreased ability to concentrate
- Poor memory
- Lack of morning erections
- Less rigid erections
- Decreased ejaculate volume
- Infertility

considered hypogonadal. The Massachusetts Male Ageing Study (MMAS), estimated that the prevalence of hypogonadism is between 6%-12% among men aged 39 to 79 years based on the presence of both symptoms and a biochemical evidence of testosterone deficiency.[4]

TABLE 2. **Populations at high risk for low serum testosterone levels**

- Type 2 diabetes
- Obesity
- Dyslipidemia
- Obstructive sleep apnea
- Coronary artery disease
- Congestive heart failure
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease
- Osteoporosis
- HIV and antiretroviral therapy use
- Chronic opioid and corticosteroid use
- Chemotherapy and radiation treatment

Hypogonadism is more likely to be associated with certain medical comorbidities.[3,5-10] Populations at high risk for low serum testosterone levels are shown in Table 2. The prevalence of symptomatic hypogonadism in these populations has been estimated to exceed 30%.[11]

Because of the expanding elderly population, the number of men that are hypogonadal will increase, and as a result, it will be more common for physicians to encounter these men in the clinic. Despite its widespread prevalence, however, it has been estimated that as few as 5% of hypogonadal men are receiving testosterone replacement therapy (TRT).[5,32,13] This could be due to a poor understanding of hypogonadism and its implications in aging men.[12,14] A study from Ontario showed that in men over the age of 65, one in 90 had been prescribed TRT but only 6% had conclusive biochemical evidence of hypogonadism.[15] Controversies over treatment risk and benefit may also contribute to the low treatment rate.[16-18]

Benefits

A wealth of data accumulated over the past 70 years has revealed that low serum testosterone levels are associated with an increased risk of cardiovascular disease, diabetes, osteoporosis, and mortality.[5-12,19,20]

Although there are very few large, long term, randomized, placebo-controlled double-blind trials to be able to categorically prove the causal relationship and direct benefit of TRT, several smaller trials consistently reveal support for the benefits of TRT in the right patient.

A US-based public health impact study predicted that testosterone deficiency could be associated with as many as 1.3 million cases of cardiovascular disease, 1.1 million cases of diabetes, and over 600,000 osteoporosis-related fractures over a 20 year period. According to the study, this would translate into $190-525 billion dollars in health care costs.[18]

Fortunately, numerous intervention trials, some randomized and some not, have shown that repletion of testosterone in hypogonadal men with these conditions may reverse or delay their progression.[21-29]

Two recently published large prospective studies with long follow up, one in a veterans population and the other in men with diabetes, found that mortality was reduced by more than half in hypogonadal men who received TRT versus a control group of similar men who did not receive this therapy.[19,20]

Cardiovascular disease

Several studies have noted an inverse relationship with lower testosterone levels associated with more severe cardiovascular disease.[8,30-33]

A large community based meta-analysis by Araujo et al investigating a cohort of 16,184 men with a mean follow up period of 9.7 years revealed that low testosterone levels were associated with an increased risk of cardiovascular-related mortality with an HR of 1.35, (95% CI, 1.13-1.62; $p < .001$).[34]

Multiple randomized controlled trials have suggested that TRT has a protective effect on rates of myocardial infarction (MI) with an increased time to angina and cardiac ischemia during a treadmill test.[21,22,35]

Web et al showed that injection of physiological levels of testosterone directly into the coronary arteries led to an increase in mean coronary artery diameter and blood flow.[36]

Arterial intima-media thickness, a marker for atherosclerosis, has been shown in a dozen studies to be greater in men with lower testosterone levels.[37-48] A randomized controlled trial by Aversa et al demonstrated significant reductions in carotid intima-media thickness with TRT versus placebo in hypogonadal men.[48]

In a study of severely obese hypogonadal men randomized to 54 weeks of diet and exercise alone versus diet and exercise with TRT, testosterone-therapy-treated men had significant improvements in cardiac ejection fraction, carotid intima-media thickness, endothelial function, and epicardial fat burden. Of note, cessation of testosterone therapy resulted in return of cardiovascular factors to baseline 24 weeks later, despite ongoing exercise and dietary measures.[37]

Diabetes

Large population-based studies have revealed that men with the lowest levels of endogenous serum testosterone concentrations have twice the risk of developing diabetes.[49-51] Data from HIM study revealed that as many as 50% of diabetic men were testosterone deficient.[50] In the Rancho Bernado study that followed a population-based cohort of 6629 men for up to 20 years, testosterone levels were inversely related to weight, body mass index, fasting glucose, and serum insulin levels.[7]

Several randomized controlled trails have noted consistent metabolic improvements with TRT, through decreases in total and visceral body fat, decreases in insulin resistance and improvements in glycosylated hemoglobin levels and glycemic control.[52-55]

Bone and muscle health

Osteoporosis is a source of considerable morbidity and mortality in elderly men. Almost 30% of all hip fractures are in men and men are twice as likely as women to die in hospital after a hip fracture.[5,56,57] A nursing home study revealed that 66% of elderly men who had experienced a hip fracture were testosterone deficient.[58] Repletion of testosterone to physiological levels has been shown to significantly improve bone mineral density. A randomized placebo-controlled study by Amory et al in hypogonadal men demonstrated bone mineral density increased 3% to 4% in the hip and there was an impressive 10% increase in bone mineral density of the spine with TRT over a 36 month period.[59]

Numerous randomized placebo controlled trials have revealed that TRT given to hypogonadal men results in increased lean muscle mass with improvements in strength and endurance.[60-68] In some older, frail men with limited mobility, significant functional gains have been demonstrated with appropriate testosterone replacement.[60] A study by Amory et al suggests that TRT in testosterone deficient men may be of use in populations that are at risk of developing a muscle-wasting catabolic state. Treating testosterone-deficient men with TRT before knee replacement surgery improved functional independence and thus recovery afterwards.[69]

Other

Repletion of testosterone in hypogonadal men has been shown to improve several domains of sexual function, including libido, erectile function, and sexual performance.[6,24,70-75] When regular TRT was added to therapy with "on demand" phosphodiesterase-type 5 (PDE-5) inhibitors, hypogonadal men who were refractory to treatment with a PDE-5 inhibitor alone recovered the ability to have an erection.[73] Improvements in cognitive function, mood, vitality, and quality of life have also been accredited to TRT.[76-82]

Risks and realties

Restoring testosterone to physiological levels is generally very well tolerated and associated with few if any side effects. The intention is to bring the testosterone level back to the normal or high-normal range. Dosing to achieve levels above the normal range, however, can be cause for more serious concern and potential side effects.

Cardiovascular morbidity

Only four trials to date have suggested an increased risk of cardiovascular morbidity with TRT. Two of these studies used supra-physiologic doses of testosterone.[83,84] The other two had major design

and interpretation flaws.[85,86] The Food and Drug Administration (FDA) confirmed these inaccuracies after official review. In fact, when the raw data was properly reinterpreted, TRT was actually shown to have a protective effect.[87]

The largest meta-analysis to date which examined 75 placebo-controlled studies suggested that TRT was not related to any increase in cardiovascular risk and instead demonstrated a benefit in those with metabolic derangements.[88]

A recent study reported results in more than 300 men who were randomized to placebo or TRT. The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a placebo-controlled, double-blind, parallel-group, 1:1 randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100 ng/dL to 400 ng/dL; free testosterone < 50 pg/mL), who were recruited at three US centers. Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium. There was no increase in coronary artery calcium or carotid intima-media thickness (CIMT) after 3 years of testosterone therapy in the TRT arm compared to placebo.[89]

Congestive heart failure

There is a concern for instigating volume overload in treating patients with a history of congestive heart failure (especially those with poorly controlled disease). Fluid retention is a possible side effect of TRT.[16,90-92] Perhaps more concerning though, is that a link between untreated testosterone deficiency and increased mortality due to congestive heart failure has been suggested.[93,94] Furthermore, several small prospective randomized controlled trials have demonstrated significant functional improvements in exercise capacity and peak oxygen consumption, without any adverse cardiovascular effect, in hypogonadal men given testosterone replacement over placebo.[95-99] However, until there are larger trials to dictate otherwise, in patients with poorly controlled congestive heart failure, testosterone treatment is contraindicated.[1,90]

Lipid profiles

With respect to serum lipids, the available data is inconsistent, but effect on lipids seems to depend on the amount of testosterone administered. While supraphysiologic doses of testosterone may have a negative effect on serum cholesterol through a reduction in high-density lipoprotein (HDL), dosing to achieve the eugonadal range of testosterone does not seem to affect lipid profiles.[28,76,100,101]

Polycythemia

Erythropoiesis is stimulated by increased testosterone concentrations in boys at puberty, so that adult males, on average, have higher hemoglobin levels than adult females. The decrease in hemoglobin levels seen in elderly men is hypothesized to be secondary to declining testosterone levels.[102] Canadian clinical practice guidelines recommend testosterone replacement in hypogonadal men with anemia of unknown origin. Although the restoration of hemoglobin levels to normal values may be beneficial, elevation to concentrations above the physiological range may lead to a dangerous increase in blood viscosity that could cause thrombosis. This is particularly important in those who are at high risk, such as elderly men with atherosclerosis and vascular insufficiency. The Endocrine Society recommends against testosterone replacement in those men with a baseline hematocrit > 50 for fear of worrisome erythrocytosis.[90] Of note, it has been demonstrated that the incidence of erythropoiesis is often directly related to the dosage of testosterone administered, so that usually only supra-physiologic concentrations of testosterone are of significant concern.[103] Studies suggest that these higher levels are more commonly seen with intramuscular (IM) dosing.[24,76] One multicenter, randomized, parallel-group study demonstrated that 43.8% of hypogonadal men receiving IM testosterone injections versus 15.4% of hypogonadal men who received a testosterone patch had at least one documented elevated hematocrit value over a 24 week study period.[76] Another prospective study observed erythrocytosis in only 5.5% of patients using a testosterone patch over 36 months with most changes in hemoglobin and hematocrit values limited to the first 3 months of treatment.[23] Continued follow up screening is nevertheless recommended, with cessation of treatment if levels are concerning (hematocrit > 54).[90]

One double-blind, placebo-controlled, randomized, parallel-group study using IM testosterone suggested testosterone may stimulate thromboxane A2 (TXA2), a vasoconstrictor and platelet pro-aggregatory agent. It was hypothesized that this may contribute to the thrombogenicity and RBC adhesion of androgenic steroids.[104] Of note however, the treatment duration was short, the sample size was small and the patients were not testosterone deficient at baseline. Furthermore, this was purely a biochemical analysis with no clinical end points. Larger long term randomized controlled trials are therefore necessary to confirm this hypothesis.

Benign prostatic hyperplasia (BPH)

Although it is well recognized that benign prostatic growth is stimulated by the presence of androgens, multiple studies including several randomized controlled trials have failed to show an increase in voiding symptoms or other complications such as urinary retention during TRT in hypogonadal men.[25,55,59,60,76,104-111] A slight increase in prostate size was seen in some trials of TRT, but flow rates and post void residual volumes did not change significantly when the normal physiological range of testosterone was achieved. This paradox may be due to the poor correlation between prostate volume and urinary symptoms. Clinicians should nevertheless be aware of this slight increase in prostate size with TRT, and AUA symptom scores should be monitored. It is suggested that caution be exerted with TRT for patients with severe lower urinary tract symptoms (IPSS > 19) at baseline.[90] If voiding symptoms should arise during treatment with TRT, one may consider additional medical management (with a 5-alpha reductase inhibitor or alpha blocker) and/or a urological consultation.

Prostate cancer

Huggins and Hodges demonstrated, over 70 years ago, that suppression of testosterone levels leads to a regression of prostate cancer.[112] It has since been the practice to reduce blood levels of androgen to castrate values in men with metastatic prostate cancer in order to delay cancer progression. Despite this relationship, however, years of research have failed to demonstrate any compelling evidence that TRT in hypogonadal men increases the risk of prostate cancer above that in the general population.[24-27,76,100,103,105,113-118] In fact, it has been hypothesized that untreated hypogonadal men, in contrast to eugonadal and castrated men, may be at an increased risk of prostate cancer.[73,119-124] This relationship has been described through a saturation model, which describes that prostate cancer growth is exquisitely sensitive to variations in serum testosterone levels below a certain threshold.[125,126] This is based on the fact that the availability of binding sites for testosterone to androgen receptors is limited. When androgen receptors are saturated, further increases in testosterone levels do not lead to further androgen receptor binding, and thus this fails to stimulate prostate cancer growth. The approximate threshold beyond which androgen receptors are saturated was suggested in a series by Morgentaler and Rhoden who reported that the risk of a positive prostate biopsy was 21% in men with a testosterone level < 250 ng/mL versus 12% in men with a testosterone level > 250 ng/mL.[124] Furthermore, in a retrospective analysis by Park et al, testosterone deficiency (< 300 ng/mL) was noted to be an independent risk factor for high-grade prostate cancer on biopsy.[127] Low preoperative testosterone levels have also been associated with poor prognostic factors at the time of radical prostatectomy, including higher Gleason score, positive surgical margins, extraprostatic extension, and seminal vesicle invasion. Postoperative biochemical failure has also been linked to low pre-treatment testosterone levels.[120,122,128-135]

It is well accepted that metastatic prostate cancer is a contraindication to TRT.[1,90] There is evidence, however, to suggest that TRT is safe in hypogonadal men who have been "cured" of prostate cancer with surgery or radiation treatment for localized disease. Among with multiple benefits of feelings of well-being and increased energy, improvements in erectile function, a common post-treatment difficulty, have been noted with TRT.[136] Although most of the evidence comes from small case series, results demonstrate that even men with poor prognostic features such as higher Gleason scores (8-10) can be successfully treated for long durations without biochemical recurrence of prostate cancer.[136-143] It has been suggested that a disease-free interval of at least 1 year or more should precede any TRT. It has also been recommended that these patients be referred to a specialist for expert assessment and close follow up.[1]

Fertility and secondary sex characteristics

Fertility is significantly compromised during TRT, as a secondary effect due to a down regulation of gonadotropins.[16,91,92,144] Testicular size and consistency also decrease due to a lack of trophic (FSH/LH) stimulation. These effects are usually reversible with the cessation of therapy; however, it is recommended not to treat patients with TRT if they are interested in maintaining fertility more than in improving symptoms of hypogonadism.[1,90]

Gynecomastia and breast cancer

Breast tenderness and swelling may also occur due to the aromatization of testosterone into estradiol; however, the incidence is rare with doses used to achieve the normal range of testosterone.[16,91,92] These effects are usually reversible with cessation of therapy. Interestingly, it is widely recommended not to give TRT to men with a history of breast cancer due to the fear that aromatized androgens may stimulate breast cancer proliferation.[1,90] This direct causal effect, however, has never been studied in hypogonadal men who were given TRT. In fact, in-vitro studies have actually revealed that androgens have apoptotic and

anti-proliferative effects on breast cancer growth.[145-147] Furthermore, androgen therapy, both with or without an aromatase inhibitor, has been suggested to have a protective effect against breast cancer.[148-150] Recent data has revealed that neoadjuvant therapy with testosterone and an aromatase inhibitor given to hormone positive breast cancer patients significantly reduces tumor size for a more successful surgical outcome.[151] Given the current level of evidence in the literature, however, a history of breast cancer remains a contraindication to TRT in clinical practice guidelines.[1,90]

Sleep apnea

Testosterone levels play a role in sleep architecture, which is suggested to be related to centrally mediated breathing controls rather than anatomical factors.[152-154] The Endocrine Society Clinical Practice Guidelines recommend against TRT in men with untreated, severe obstructive sleep apnea.[90] Most of the data to corroborate this recommendation, however, comes from case reports and small studies. Given the available evidence, it appears that while supra-physiologic levels of testosterone may have a deleterious effect on sleep patterns, restoring testosterone to the eugonadal range does not seem to have these negative consequences.[152-165] In fact, repletion of testosterone may be of benefit with regards to sleep, since sleep apnea has been suggested in several publications to be more common in the hypogonadal population versus eugonadal controls.[114-128] Until further evidence is available through large prospective trials, however, severe untreated obstructive sleep apnea remains a contraindication to testosterone replacement.[90]

Hepatic effects

The risk of hepatotoxicity with testosterone supplementation is historical and limited to oral preparations that are metabolized by the liver.[166] The newer oral forms of testosterone are absorbed by the lymphatic circulation, bypassing the portal system and subsequent hepatic metabolism that accounts for toxic effects. Routine monitoring of liver enzymes for Canadian and US approved formulations of TRT is therefore unnecessary.[16,167] Although this route of delivery may seem ideal, the bioavailability of the dose administered depends on the ingestion of a fatty meal and therefore routine use can be impractical.

Skin reactions

Acne and oily skin are infrequent with physiological doses of testosterone.[16,91,92] Local skin reactions at the delivery site are more commonly a concern with transdermal testosterone therapy. Erythema and pruritus are the usual reactions and are much more prevalent with patches (66%) than with gel preparations (5%) as demonstrated in a prospective multicenter double-blind randomized study by Wang et al.[103]

Conclusion

Testosterone deficiency syndrome is a syndrome related to low testosterone levels, which often occur later in life, which has been linked to considerable morbidity and health care cost burden. Due to the increasing life expectancy of the population, the number of symptomatic, hypogonadal men presenting to our clinics is also expected to increase. Fortunately, evidence suggests that TRT is quite safe and effective at helping to treat or delay time to progression of morbidities associated with this condition. It is crucial, however, that clinicians are aware not only of the benefits, but also of the possible risks associated with treatment so that patients are appropriately selected and follow up is adequate. Given our current level of evidence, contraindications to TRT include polycythemia (HCT > 54), metastatic prostate cancer, a history of breast cancer, poorly controlled congestive heart failure, untreated severe obstructive sleep apnea, as well as those desiring fertility over symptomatic treatment.

Disclosure

Dr. Jacob Hassan has no disclosure.
Dr. Jack Barkin is a speaker and investigator for Glaxo, Actavis, Pfizer, Astellas, Merus Labs, Allergan, Janssen, Ferring, NeoTract and Merck. □

References

1. Morales A, Bebb R, Manjoo P et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline *CMAJ* 2015;187(18):1369-1377.
2. Morley JE, Charlton E, Patrick P et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000;49(9):1239-1242.
3. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM Study. *Int J Clin Pract* 2006;60(7):762-769.

4. Araujo AB, Esche GR, Kupelian V et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007;92(11):4241-4247.
5. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract* 2010;64(6):682-696.
6. Bhasin S, Cunningham GR, Hayes SJ et al. Task Force, Endocrine Society. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-2559.
7. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008;93(1):68-75.
8. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab* 2002;87(8):3632-3639.
9. Yeap BB, Hyde Z, Norman PE, Chubb SAP, Golledge J. Associations of total testosterone, sex hormone-binding globulin, calculated free testosterone, and luteinizing hormone with prevalence of abdominal aortic aneurysm in older men. *J Clin Endocrinol Metab* 2010;95(3):1123-1130.
10. Tivesten A, Vandenput L, Labrie F et al. Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab* 2009;94(7):2482-2488.
11. Zarotsky V, Huang M-Y, Carman W et al. Systematic literature review of the epidemiology of nongenetic forms of hypogonadism in adult males. *J Hormones* 2014;2014:190347.
12. Hall SA, Araujo AB, Esche GR et al. Treatment of symptomatic androgen deficiency. *Arch Intern Med* 2008;168(10):1070-1076.
13. Seftel AD. Male hypogonadism. Part I: epidemiology of hypogonadism. *Int J Impot Res* 2006;18(2):115-120.
14. Little D. Andropause: Identifying, treating, and following the patient. *Geriatrics & Aging* 2004;7:13-18.
15. Piszcek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.
16. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004;350(5):482-492.
17. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc* 2015;90(2):224-251.
18. Moskovic DJ, Araujo AB, Lipshultz LI, Khera M. The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. *J Sex Med* 2013;10(2):562-569.
19. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97(6):2050-2058.
20. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169(6): 725-733.
21. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 2000;102(16):1906-1911.
22. Webb CM, Adamson DL, de Zeigler D, Collins P. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol* 1999;83(3):437-439:A9.
23. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J* 2000;21(11):890-894.
24. Snyder PJ, Peachey H, Berlin JA et al. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2670-2677.
25. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2001;56(5):M266-M272.
26. Snyder PJ, Peachey H, Hannoush P et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(6):1966-1972.
27. Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997;82(6):1661-1667.
28. Snyder PJ, Peachey H, Berlin JA et al. Effects of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *Am J Med* 2001;111(4):255-260.
29. Isidori AM, Giannetta E, Greco EA et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(3):280-293.
30. Dobrzycki S, Serwatka W, Nadlewski S et al. An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males. *J Med Invest* 2003;50 (3-4):162-169.
31. Rosano GM, Sheiban I, Massaro R et al. Low testosterone levels are associated with coronary artery disease in male patients with angina. *Int J Impot Res* 2007;19(2):176-182.
32. Li L, Guo CY, Jia EZ et al. Testosterone is negatively associated with the severity of coronary atherosclerosis in men. *Asian J Androl* 2012;14(6):875-878.
33. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb* 1994;14(5):701-706.
34. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96(10):3007-3019.
35. Rosano GM, Leonardo F, Pagnotta P et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease [published correction appears in *Circulation* 2000;101(5):584]. *Circulation* 1999;99(13):1666-1670.
36. Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation* 1999;100(16): 1690-1696.
37. Francomano D, Bruzziches R, Barbaro G, Lenzi A, Aversa A. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. *J Endocrinol Invest* 2014;37(4):401-411.
38. De Pergola G, Pannacciulli N, Ciccone M, Tartagni M, Rizzon P, Giorgino R. Free testosterone plasma levels are negatively associated with the intima-media thickness of the common carotid artery in overweight and obese glucose- tolerant young adult men. *Int J Obes Relat Metab Disord* 2003;27(7):803-807.
39. Fu L, Gao QP, Shen JX. Relationship between testosterone and indexes indicating endothelial function in male coronary heart disease patients. *Asian J Androl* 2008;10(2):214-218.
40. Fukui M, Kitagawa Y, Nakamura N et al. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. *Diabetes Care* 2003;26(6):1869-1873.
41. Mäkinen J, Järvisalo MJ, Pöllänen P et al. Increased carotid atherosclerosis in andropausal middle-aged men. *J Am Coll Cardiol* 2005;45(10):1603-1608.

42. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation* 2004;109(17):2074-2079.
43. Soisson V, Brailly-Tabard S, Empana JP et al. Low plasma testosterone and elevated carotid intima-media thickness: importance of low-grade inflammation in elderly men. *Atherosclerosis* 2012;223(1):244-249.
44. Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bønaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. *J Intern Med* 2006;259(6):576-582.
45. Tsujimura A, Yamamoto R, Okuda H et al. Low serum free testosterone level is associated with carotid intima-media thickness in middle-aged Japanese men. *Endocr J* 2012;59(9): 809-815.
46. van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. *Am J Epidemiol* 2003;157(1):25-31.
47. Vikan T, Johnsen SH, Schirmer H, Njølstad I, Svartberg J. Endogenous testosterone and the prospective association with carotid atherosclerosis in men: the Tromsø study. *Eur J Epidemiol* 2009;24(6):289-295.
48. Aversa A, Bruzziches R, Francomano D et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;7(10):3495-3503.
49. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 2004;89(11):5462-5468.
50. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006;60(7):762-769.
51. Dhindsa S, Miller MG, McWhirter CL et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33(6):1186-1192.
52. Jones TH, Arver S, Behre HM et al; TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 2011;34(4):828-837.
53. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glyce-mic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(6):726-733.
54. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 2006; 154(6):899-906.
55. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study [published correction appears in *Clin Endocrinol (Oxf)* 2011;75(2):275]. *Clin Endocrinol (Oxf)* 2010;73(5):602-612.
56. Ebeling PR. Clinical practice. Osteoporosis in men. *N Engl J Med* 2008;358(14):1474-1482.
57. Gronholz MJ. Prevention, diagnosis, and management of osteoporosis-related fracture: a multifactoral osteopathic approach. *J Am Osteopath Assoc* 2008;108(10):575-585.
58. Abbasi AA, Rudman D, Wilson CR et al. Observations on nursing home residents with a history of hip fracture. *Am J Med Sci* 1995;310(6):229-234.
59. Amory JK, Watts NB, Easley KA et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89(2):503-510.
60. Srinivas-Shankar U, Roberts SA, Connolly MJ et al. 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* 2010;95(2):639-650.
61. Page ST, Amory JK, Bowman FD et al. 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* 2005;90(3): 1502-1510.
62. Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20(4):378-387.
63. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab* 2003;88(7): 3167-3176.
64. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R; North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 2003;88(6):2673-2681.
65. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low- normal gonadal status. *J Gerontol A Biol Sci Med Sci* 2003;58(7):618-662
66. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab* 2008;93(1):139-146.
67. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial [published correction appears in *JAMA* 2008;299(6):634]. *JAMA* 2008;299(1):39-52.
68. Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12- month randomized controlled trial. *J Clin Endocrinol Metab* 1997;82(6):1661-1667.
69. Amory JK, Chansky HA, Chansky KL et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. *J Am Geratr Soc* 2002;50(10): 1698-1701.
70. Bhasin S, Basaria S. Diagnosis and treatment of hypogonadism in men. *Best Pract Res Clin Endocrinol Metab* 2011;25(2):251-270.
71. Isidori AM, Giannetta E, Gianfrilli D et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(4):381-394.
72. Permpongkosol S, Tantirangsee N, Ratana-olarn K. Treatment of 161 men with symptomatic late onset hypogonadism with long-acting parenteral testosterone undecanoate: effects on body composition, lipids, and psychosexual complaints. *J Sex Med* 2010;7(11):3765-3774.
73. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172(2): 658-663.
74. Tenover JL. Male hormone replacement therapy including "andropause." *Endocrinol Metab Clin North Am* 1998;27(4): 969-987.

75. Kim YC. Testosterone supplementation in the aging male. *Int J Impot Res* 1999;11(6):343-352.
76. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacoki- netics, efficacy, and safety of a permeation- enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999;84(10):3469-3478.
77. Cherrier MM, Asthana MD, Plymate S et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology* 2001;57(1):80-88.
78. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab* 2002;87(11):5001-5007.
79. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality- of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med* 2013;10(6):1612-1627.
80. Tong SF, Ng CJ, Lee BC et al. Effect of long-acting testosterone undecanoate treatment on quality of life in men with testosterone deficiency syndrome: a double blind randomized controlled trial. *Asian J Androl* 2012;14(4):604-611.
81. Pexman-Fieth C, Behre HM, Morales A, Kan-Dobrosky N, Miller MG. A 6-month observational study of energy, sexual desire, and body proportions in hypogonadal men treated with a testosterone 1% gel. *Aging Male* 2014;17(1):1-11.
82. Yassin DJ, Doros G, Hammerer PG, Yassin AA. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life. *J Sex Med* 2014;11(6):1567-1576.
83. Basaria S, Coviello AD, Travison TG et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-122.
84. Copenhagen Study Group for Liver Diseases. Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. *Hepatology* 1986;6(5):807-813.
85. Vigen R, O'Donnell CI, Barón AE et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels [published correction appears in *JAMA* 2014;311(9):967]. *JAMA* 2013; 310(17):1829-1836.
86. Finkle WD, Greenland S, Ridgeway GK et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PloS One* 2014;9(1):e85805.
87. Miner M, Barkin J, Rosenberg MT. Testosterone deficiency: myth, facts, and controversy. *Can J Urol* 2014;21(Suppl 2):39-54.
88. Corona G, Maseroli E, Rastrelli G et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014;13(10):1327-1351.
89. Basaria S, Harman SM, Travison TG et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. *JAMA* 2015;314(6):570-581.
90. Bhasin S, Cunningham GR, Hayes SJ et al. Task Force, Endocrine Society. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-2559.
91. Fernández-Balsells MM, Murad MH, Barwise A et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas : a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96(4):905-912.
92. Am Society Androl Position Statement: Testosterone Deficiency. *J Androl* 2006;27(2):133-134.
93. Wehr E, Pilz S, Boehm BO, März W, Grammer T, Obermayer-Pietsch B. Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography. *Eur J Heart Fail* 2011;13(5):482-488.
94. Jankowska EA, Biel B, Majda J et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation* 2006;114(17):1829-1837.
95. Caminiti G, Volterrani M, Iellamo F et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009;54(10):919-927.
96. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006;27(1):57-64.
97. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. *Heart* 2004;90(4):446-447.
98. Lellamo F, Volterrani M, Caminiti G et al. Testosterone therapy in women with chronic heart failure: a pilot double- blind, randomized, placebo-controlled study. *J Am Coll Cardiol* 2010; 56(16):1310-1316.
99. Wu HY, Wang XF, Wang JH, Li JY. Testosterone level and mortality in elderly men with systolic chronic heart failure. *Asian J Androl* 2011;13(5):759-763.
100. Singh AB, Hsia S, Alaupovic P et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. *J Clin Endocrinol Metab* 2002;87(1):136-143.
101. Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med* 2001;111(4): 261-269.
102. Basaria S, Dobs AS. Risks versus benefits of testosterone therapy in elderly men. *Drugs Aging* 1999;15(2):131-142.
103. Wang C, Swerdloff RS, Iranmanesh A et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-2853.
104. Comhaire FH. Andropause: hormone replacement therapy in the aging male. *Eur Urol* 2000;38(6):655-662.
105. Krieg M, Nass R, Tunn S. Effect of aging on endogenous level of 5a-dihydrotestosterone, testosterone, estradiol, and estrone in epithelium and stroma of normal and hyperplastic human prostate. *J Clin Endocrinol Metab* 1993;77(2):375-381.
106. Pechersky AV, Mazurov VI, Semiglazov VF, Karpischenko AI, Mikhailichenko VV, Udintsev AV. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestos- terone, oestradiol and prostate volume. *Int J Androl* 2002;25(2):119-125.
107. Marcelli M, Cunningham GR. Hormonal signaling in prostatic hyperplasia and neoplasia. *J Clin Endocrinol Metab* 1999;84(10):3463-3468.
108. Slater S, Oliver RTD. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. *Drugs Aging* 2000;17(6):431-439.
109. Hildreth KL, Barry DW, Moreau KL et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab* 2013;98(5):1891-1900.
110. Del Fabbro E, Garcia JM, Dev R et al. Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial. *Support Care Cancer* 2013;21(9):2599-2607.

111. Tan WS, Low WY, Ng CJ et al. Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomized controlled study. *BJU Int* 2013;111(7):1130-1140.
112. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. *Arch Surg* 1941;43:209-223.
113. Calof OM, Singh AB, Lee ML et al. 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* 2005;60(11):1451-1457.
114. Carter HB, Pearson JD, Metter EJ et al. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate* 1995;27(1):25-31.
115. Heikkila R, Aho K, Heliovaara M et al. Serum testosterone and sex hormone-bind- ing globulin concentrations and the risk of prostate carcinoma: a longitudinal study. *Cancer* 1999;86(2):312-315.
116. Hsing AW. Hormones and prostate cancer: what's next? *Epidemiol Rev* 2001;23(1):42-58.
117. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol* 1996;77(3):433-440.
118. Vermeulen A. Androgen replacement therapy in the aging male — a critical evaluation. *J Clin Endocrinol Metab* 2001;86(6):2380-2390.
119. Morgentaler A, Bruning CO III, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. *JAMA* 1996;276(23):1904-1906.
120. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol* 2000;163(3):824-827.
121. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous Hormones and Prostate Cancer Collaborative Group. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008;100(3):170-183.
122. Yamamoto S, Yonese J, Kawakami S et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. *Eur Urol* 2007;52(3):696-701.
123. Platz EA, Leitzmann MF, Rifai N. Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era. *Cancer Epidemiol Bio Prev* 2005;14(5):1262-1269.
124. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen of 4.0 ng/ml or less. *Urology* 2006;68(6):1263-1267.
125. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the Saturation Model and the limits of androgen-dependent growth. *Eur Urol* 2009;55(2):310-320.
126. Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M. Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011;185(4):1256-1260.
127. Park J, Cho SY, Jeong SH et al. Low testosterone level is an independent risk factor for high-grade prostate cancer detection at biopsy. *BJU Int* 2015. Epub ahead of print.
128. Garcia-Cruz E, Piqueras M, Huguet J et al. Low testosterone levels are related to poor prognosis factors in men with prostate cancer prior to treatment. *BJU Int* 2012;110(11 Pt B): E541E546.
129. Botto H, Neuzillet Y, Lebret T et al. High incidence of predominant Gleason pattern 4 localized prostate cancer is associated with low serum testosterone. *J Urol* 2011;186(4):1400-1405.
130. Morgentaler A. Turning conventional wisdom upside-down: low serum testosterone and high-risk prostate cancer. *Cancer* 2011;117(17):3885-3888.
131. Salonia A, Gallani A, Briganti A. Preoperative hypogonadism is not an independent predictor of high-risk disease in patients undergoing radical prostatectomy. *Cancer* 2011;117(17):3953-3962.
132. Cabral PH, Iwamoto MW, Fanni VS, Barros Lda R, Cardoso SN, Mello LF, Glina S. Study of testosterone as a predictor of tumor aggressiveness in patients with prostate cancer. *Int Braz J Urol* 2013;39(2):173-181.
133. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *J Urol* 2005;174(6):2178-2180.
134. Pichon A, Neuzillet Y, Botto H et al. Preoperative low serum testosterone is associated with high-grade prostate cancer and an increased Gleason score upgrading. *Prostate Cancer Prostatic Dis* 2015;18(4):382-387.
135. Isom-Batz G, Bianco FJ, Jr, Kattan MW et al. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *J Urol* 2005;173(6):1935-1937.
136. Balbontin FG, Moreno SA, Bley E et al. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. *BJU Int* 2014;114(1):125-130.
137. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 2005;173(2):533-536.
138. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 2004;172(3):920-922.
139. Khera M, Grober ED, Najari B et al. Testosterone replacement therapy following radical prostatectomy. *J Sex Med* 2009;6(4): 1165-1170
140. Pastuszak AW, Pearlman AM, Godoy G et al. Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *Int J Impot Res* 2013;25(1):24-28.
141. Pastuszak AW, Pearlman AM, Lai WS et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol* 2013;190(2):639-644.
142. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007;109(3):536-541.
143. Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int* 2009;103(1): 62-64.
144. Bagatell CJ, Bremner WJ. Androgens in men — uses and abuses. *N Engl J Med* 1996;334(11):707-714.
145. Dimitrakakis C, Zhou J, Wang J et al. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause* 2003;10(4):292-298.
146. Hickey TE, Robinson JL, Carroll JS, Tilley WD. Minireview: the androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene. *Mol Endocrinol* 2012;26(8): 1252-1267.
147. Eigeliene N, Elo T, Linhala M, Hurme S, Erkkola R, Härkönen P. Androgens inhibit the stimulatory action of 17ß-estradiol on normal human breast tissue in explant cultures. *J Clin Endocrinol Metab* 2012;97(7):E1116-E1127.
148. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in post-menopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11(5):531-535.
149. Glaser R, Dimitrakakis C. Reduced incidence of breast cancer in women adherent to testosterone or testosterone-anastrozole hormone therapy: updated interim analysis. In: 10th EMAS congress, May 2015. 2015 (abstract/poster P124).

150. Glaser RL, Dimitrakakis C. Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: a prospective, observational study. *Maturitas* 2013;76(4):342-349.
151. Glaser RL, Dimitrakakis C. Rapid response of breast cancer to neoadjuvant intra- mammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer. *Menopause* 2014;21(6):673-678.
152. Wittert G. The relationship between sleep disorders and testosterone in men. *Asian J Androl* 2014;16(2):262-265.
153. Wittert G. The relationship between sleep disorders and testosterone. *Curr Opin Endocrinol Diabetes Obes* 2014;21(3):239-243.
154. Schneider BK, Pickett CK, Zwillich CW et al. Influence of testosterone on breathing during sleep. *J Appl Physiol* 1986;61(2): 618-623.
155. Matsumoto AM, Sandblom RE, Schoene RB et al. Testosterone replacement in hypo- gonadal men: effects on obstructive sleep apnea, respiratory drives, and sleep. *Clin Endocrinol (Oxf)* 1985;22(6):713-721.
156. Liu PY, Yee B, Wishart SM et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metab* 2003;88(8):3605-3613.
157. Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? *J Sex Med* 2007;4(5): 1241-1246.
158. Killick R, Wang D, Hoyos CM et al. The effects of testosterone on ventilatory responses in men with obstructive sleep apnoea: a randomised, placebo-controlled trial. *J Sleep Res* 2013;22(3):331-336.
159. Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. *Clin Endocrinol (Oxf)* 2012;77(4):599-607.
160. Hammoud AO, Walker JM, Gibson M et al. Sleep apnea, reproductive hormones and quality of sexual life in severely obese men. *Obesity (Silver Spring)* 2011;19(6):1118-1123.
161. Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. *J Endocrinol Invest* 2003;26(6):493-498.
162. Luboshitzky R, Lavie L, Shen-Orr Z, Herer P. Altered luteinizing hormone and testosterone secretion in middle-aged obese men with obstructive sleep apnea. *Obes Res* 2005;13(4):780-786.
163. Canguven O, Salepci B, Albayrak S et al. Is there a correlation between testosterone levels and the severity of the disease in male patients with obstructive sleep apnea? *Arch Ital Urol Androl* 2010;82(4):143-147.
164. Molina FD, Suman M, Carvalho TB et al. Evaluation of testosterone serum levels in patients with obstructive sleep apnea syndrome. *Braz J Otorhinolaryngol* 2011;77(1):88-95.
165. Barrett-Connor E, Dam TT, Stone K et al. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. *J Clin Endocrinol Metab* 2008;93(7):2602-2609.
166. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet* 1977;2(8032):262-263.
167. Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men (CME). *J Sex Med* 2011;8(3): 639-654.