Androgen deficiency in the aging male: a guide to diagnosis and testosterone replacement therapy

Mathew C. Raynor, MD,[1] Culley C. Carson, MD,[2] Matthew D. Pearson, MD,[2] Jeffrey W. Nix, MD[2]

[1]Department of Urology, Tulane University Health Sciences Center, New Orleans, Louisiana, USA
[2]Division of Urology, University of North Carolinam, Chapel Hill, North Carolina, USA

RAYNOR MC, CARSON CC, PEARSON MD, NIX JW. Androgen deficiency in the aging male: a guide to diagnosis and testosterone replacement therapy. The Canadian Journal of Urology. 2007;14(Supplement 1):63-68.

A steady decline in androgen levels occurs in males as they age. Evidence suggests that this decline may be at least partially responsible for a variety of physical and mental changes associated with the aging process. For instance, abnormally low levels of androgens can lead to profound changes in bone density, body composition, as well as sexual and cognitive function. Testosterone replacement has been shown to produce improvements in many of these areas. However, this practice is not without risks, both proven and theoretic. Also, the diagnosis of androgen deficiency and the decision to treat is not always straightforward. The purpose of this article is to familiarize the clinician with issues associated with androgen deficiency in the aging male. The clinical symptoms of androgen deficiency as well as the risks and benefits of androgen replacement will be discussed. This should help clinicians better identify those patients in whom testosterone replacement therapy should be considered.

Key Words: androgen, testosterone replacement therapy, aging male

Background

Both cross-sectional and longitudinal studies demonstrate a progressive decline in androgen levels as men age. When this biochemical decline is associated with any of a number of clinical symptoms, the entity has been described as androgen deficiency in the aging male (ADAM). Other terms used to describe this phenomenon include andropause, male menopause, male climacteric syndrome, and hypogonadism. Symptoms associated with this syndrome include those typically associated with aging such as osteoporosis, decreased cognitive function and mood, change in body composition, and declining libido and sexual function. Hormone replacement therapy can improve many of these symptoms, but therapy is not without risks. Possible side effects of testosterone replacement include hepatotoxicity, alterations in lipid profiles, sleep and mood disorders, and prostate hyperplasia or cancer. Therefore, hormone replacement therapy mandates periodic evaluation to monitor side effects of the treatment.

Address correspondence to Dr. Culley C. Carson, UNC Division of Urology, 2140 Bioinformatics Bldg CB 7235, Chapel Hill NC 27599-7235 USA

Epidemiology

Estimates of the prevalence of androgen deficiency in aging males are affected by the lack of a clear definition of the phenomenon. For instance, the Massachusetts Male Ageing Study used total testosterone level < 200 ng/dl or at least three symptoms of hypogonadism with a total testosterone level between 200 ng/dl and 400 ng/dl as its definition. Based on this, the study estimated the prevalence of hypogonadism to be 6.0% of men aged 40-69 years at baseline and 12.3% at follow-up assessment 7.0-10.4 year later.[1] However, a much higher prevalence of 38.7% in men > 45 years was found in the Hypogonadism in Males (HIM) study using total testosterone < 300 ng/dl as its definition.[2] More recently, a study of 1475 men in the Boston Area Community Health (BACH) survey showed the importance of considering biochemical androgen deficiency in the context of clinical symptoms. While 24% of the subjects studied had total testosterone < 300 ng/dl, nearly 47% of the subjects at least 50 years old with low testosterone were asymptomatic. In this study, crude prevalence of symptomatic androgen deficiency was found to be 5.6% among all comers with an average age of 47.3 years. However, the prevalence increased dramatically after the age of 70 to 18.4%.[3] Despite the uncertainty regarding the current prevalence of androgen deficiency, one thing that is clear is that the population of the United States is progressively aging.[4] As such, management of age-related hormonal changes will almost certainly become a more prominent part of urologic practice in the near future. Indeed, the BACH study concluded that 6.5 million American men 30 to 79 will manifest symptomatic androgen deficiency by 2025 which represents and increase of 38% compared to 2000 population estimates.[3] Conditions such as diabetes, chronic renal failure, metabolic syndrome and chronic opioid use increase the prevalence of hypogonadism.

Hormonal alterations

It is well-known that testosterone levels decline with age. Almost 20% of men aged 60-69 and 30% of men aged 70-79 have low testosterone levels.[5] In addition to a decline in total testosterone, there is also a rise in sex hormone-binding globulin that leads to a significant decline in bioavailable and free testosterone.[1,2] Luteinizing hormone (LH) levels typically increase slightly with age, likely secondary to decreased Leydig cell testosterone production.[6] However, a majority of hypogonadal elderly men will have low or inappropriately normal LH levels, indicating hypothalamic-pituitary dysfunction as well. Extra-gonadal androgens, DHEA and DHEAS, also decline with age.[7]

Diagnosis and work-up

Precisely defining androgen deficiency is more relevant to research endeavors than to clinical practice. Determination of hypogonadism requires clinical suspicion based on symptoms and exclusion of other causes. When symptomatic hypogonadism is suspected, a morning serum total testosterone level should be obtained. If abnormal or borderline (< 300 ng/dl), the test should be repeated with free T, LH, FSH, prolactin, and possibly SHBG levels. These tests aid in determining primary gonadal failure versus pituitary dysfunction. Abnormal gonadotropin values or elevated prolactin levels should prompt further evaluation of the pituitary gland with an MRI of the sella turcica for a possible pituitary adenoma. Whether the cause of low testosterone is primary gonadal failure or pituitary dysfunction, the mainstay of treatment is testosterone replacement therapy. Prior to initiating hormonal replacement therapy, a digital rectal exam should be performed. In addition, laboratory evaluation with a complete blood count, liver function tests, and PSA should be obtained. Any abnormal DRE finding or elevated PSA should prompt further investigation to rule out prostate cancer prior to beginning testosterone supplementation.

Effects of testosterone and replacement therapy

Bone

Testosterone plays a major role in bone mineral density in men.[8] However, the majority of the effect is likely due to the action of the testosterone metabolites estradiol and estrone.[9,10] However, testosterone does appear to have a direct interaction with bone cells. Testosterone has been shown to directly inhibit osteoclast formation and bone resorption whereas estrogen exerts its effects mainly through the actions of osteoblasts.[11] A recent multi-center study of 2447 men older than 65 indicated that the prevalence of osteoporosis was 12.3% in testosterone deficient men versus 6.0% in those with normal testosterone.[12] However, the effect of hypogonadism on bone is best demonstrated by examining patients with prostate cancer treated with androgen deprivation therapy. Evidence suggests that these patients are at increased risk for osteoporotic fractures and their sequelae secondary to osteopenia and osteoporosis.[13] A recent meta-analysis examined the evidence for testosterone replacement on bone and showed that there was improvement in bone mineral density in the lumbar spine as well as decreased bone resorption markers. However, none of studies included in the analysis examined fracture risk reduction with testosterone replacement therapy.[14]

Cognitive function and mood

There is a decline in cognitive function with aging.[15] The majority of cases of dementia and cognitive decline are associated with vascular changes in the central nervous system or as a result of neurodegenerative disorders such as Alzheimer's disease. There is evidence, however, indicating more than just a temporal relationship between decreasing testosterone levels and declining cognition. A prospective longitudinal study examined over 400 elderly men with respect to multiple cognitive domains and serum measurements of testosterone. Men classified as hypogonadal showed significant declines of memory and visuospatial performance as well as faster rates of decline in visual memory.[16] Recent studies have also demonstrated a link between low testosterone levels and the development of Alzheimer's disease in aging men.[17,18] This association remains to be fully elucidated, however, animal studies have shown that androgen depletion increases levels of β-amyloid protein and decreases neuronal survival in response to toxic insults.[19,20] The results of randomized, placebo-controlled studies evaluating the effect of androgen replacement on cognition have been mixed. However, a recently published literature review of the topic indicated that, in general, testosterone substitution may have moderate positive effects on selective cognitive domains (e.g. spatial ability) in older men with and without hypogonadism. This study concluded that testosterone replacement should be considered in hypogonadal men with cognitive impairment.[21]

There has also been some suggestion that testosterone supplementation may alter mood. It is well known that the incidence of depression increases with aging. Unfortunately, there have been few trials examining the relationship between low testosterone levels and depression. Randomized trials examining the relationship between testosterone supplementation in hypogonadal men and depression symptoms have shown conflicting results.[22,23] However, these trials were relatively small and larger randomized trials are needed to fully examine the benefit of testosterone supplementation in the treatment of depression for this population subset.

Body composition

Aging is associated with a decrease in skeletal muscle mass and an increase in adipose tissue.[24] These changes can result in loss of strength and mobility, leading to an increased risk of falls, fractures, decreased independence, and depression. This effect is thought to be due to a direct effect on muscle cells by testosterone as well as through stimulation of insulin-like growth factor 1.[25] Some studies have shown improvement in both leg and arm strength with testosterone supplementation[26] while other studies have shown improvement only with the coadministration of growth hormone.[27,28] Changes in muscle mass were seen both in hypogonadal elderly men and healthy younger men.[29,30] Testosterone supplementation has also been shown to affect adiposity causing a decline in fat mass and an increase in lean muscle mass[24] as well as a redistribution of adipose to the viscera and subcutaneous tissues typical of eugonadal men.[31]

Sexual function

Sexual dysfunction, in the form of erectile dysfunction or decreased libido, is a common presenting complaint in androgen deficient males. Testosterone and its metabolites are critical to sexual development, function, and desire. Testosterone appears to have greater effect on nocturnal erectile activity and maintenance of libido in hypogonadal men.[32,33] Several studies have examined the effect of testosterone supplementation on sexual function. Response rates vary dramatically in these studies as evidenced by the results of a recent meta-analysis on the subject. However, the study populations were heterogeneous and included patients with both primary and secondary testicular failure as well as some men not classified as hypogonadal.[34,35] A more recent study examining testosterone supplementation in hypogonadal men showed an initial improvement in sexual function based on the International Index of Erectile Function at 1 month of treatment, but this benefit was not maintained. There was, however, a persistent improvement in libido.[36] One critique of these results is that patient comorbidities may have contributed to the lack of persistent effect. Also, the patients in the study were not treated simultaneously with phosphodiesterase type-5 inhibitors. Coadministration of testosterone and PDE-5 inhibitors has been shown to improve erectile function in hypogonadal men.[37] Testosterone clearly has an effect on sexual function. However, the incidence of comorbid illnesses that can lead to erectile dysfunction also increases with age making the determination of the ultimate cause difficult.[38] For this reason, larger randomized studies are needed to elucidate the true contribution of testosterone replacement to erectile function in hypogonadal men.

Risks of testosterone replacement therapy

Hepatic and hematologic

Hepatotoxicity is a known side effect of some forms of testosterone replacement therapy. However, this adverse effect has only been associated with oral preparations of testosterone (alkylated forms). Manifestations include

elevated liver function tests, cholestatic hepatitis, cystic disease of the liver, and hepatocellular carcinoma. All of the newer testosterone preparations are aromatized when metabolized which prevents liver toxicity. Other forms of replacement such as testosterone undecanoate, injectable, and transdermal preparations do not appear to be associated with hepatotoxicity.[39] Androgen supplementation is also known to increase hematocrit.[40] Patients with comorbid vascular disease may have a higher risk of adverse events as a result of the polycythemia.[41] A recent meta-analysis of randomized trials of testosterone supplementation showed that polycythemia (hematocrit > 50%) was the most common adverse effect. Patients treated with testosterone were 3.6 times more likely to develop polycythemia. The intramuscular form of testosterone appears to have a higher incidence of erythrocytosis.[42] Baseline liver function tests and a complete blood count should be obtained prior to beginning supplementation. Periodic monitoring of CBC during therapy is recommended in order to assess for polycythemia. Patients developing erythrocytosis may require withholding testosterone or, occasionally, therapeutic phlebotomy.

Cardiovascular disease and lipid profile

It has been previously and incorrectly assumed that elderly men have a higher incidence of cardiovascular events than women because of the elevated levels of testosterone. However, no clinical evidence supports this assumption. In fact, evidence points to a possible beneficial effect of testosterone on cardiovascular health. Studies have failed to show any relationship between testosterone levels and angiographic evidence of coronary artery disease.[43,44] English et al, showed that men with lower bioavailable testosterone had a higher incidence of abnormal coronary angiograms.[44] In addition, a large population study showed an inverse relationship between bioavailable testosterone levels and aortic atherosclerosis.[45] A recent meta-analysis of elderly men taking testosterone showed no statistical difference in cardiovascular events when compared with placebo.[42] Lipid profile is a well-known cardiac risk marker. A meta-analysis of 19 studies involving testosterone supplementation in men with hypogonadism showed minimal decreases in total cholesterol, LDL, and HDL that did not reach statistical significance at physiologic levels of testosterone.[42] There was, however, noted to be a dose related decrease in HDL levels with testosterone supplementation. The evidence suggests a modest change in lipid levels with testosterone supplementation in hypogonadal men.[46] The effect that these changes in lipids have on cardiovascular events has yet to be elucidated.

Prostate

The prostate relies on androgens for growth and the majority of prostate cancers are hormonally responsive. Treatment of metastatic or recurrent prostate cancer routinely relies on androgen ablation. Taken at face value, this would suggest that androgen supplementation could exacerbate voiding difficulties by encouraging prostate growth. Theoretically, androgen supplementation could even unmask an indolent prostate cancer. Several studies have examined the role of testosterone supplementation and voiding difficulties. None demonstrated significant changes in urine flow rates, post-void residual volumes, or voiding symptom scores. Prostate volumes have been shown to increase in men treated with testosterone. However, studies have shown that this increase is similar to that of age matched eugonadal men.[47-49] Studies have also examined the development of prostate cancer in men treated with testosterone supplements. A review of several randomized trials showed a low number of prostate cancers detected in patients receiving testosterone. However, the number of new cases detected was similar to the prevalence in the general population.[50] A recent meta-analysis showed that prostate events occurred significantly more in treated groups. Prostate events included diagnosis of prostate cancer, elevation of PSA, and prostate biopsies. However, none of these endpoints reached statistical significance alone.[42] Regardless, patients receiving testosterone supplementation should routinely undergo digital rectal exam and PSA screening. Further study has shown that even patients at higher risk of developing prostate cancer can safely undergo testosterone replacement therapy. Rhoden et al, compared hypogonadal men with prostatic intraepithelial neoplasia (PIN) on needle biopsy with PIN- negative controls. Only one case of prostate cancer was diagnosed in the PIN+ group after 1 year of testosterone supplementation.[50] Another concern arises in the treatment of hypogonadal patients after primary treatment for prostate cancer. Historically, this was thought to be an absolute contraindication to androgen supplementation. Recently, there has been some evidence to suggest that select patients with a history of prostate cancer may safely benefit from testosterone replacement therapy. One study retrospectively reviewed seven patients with organ-confined disease treated with radical retropubic prostatectomy that were diagnosed with hypogonadism. After initiation of testosterone supplementation, no evidence of recurrence (based on PSA) was documented.[51] Similarly, a cohort often patients were studied and also showed no evidence of disease recurrence after a median follow-up of 19

months.[52] Larger randomized trials are needed to further assess the risk of prostate cancer development during testosterone replacement therapy.

Other risks

There are several other risks associated with testosterone replacement therapy. Skin reactions may occur with transdermal testosterone delivery systems. This is more commonly seen with patches than with gel formulations. Testicular size and fertility will decrease with supplementation as the pituitary-gonadal axis is suppressed with exogenous androgen. Gynecomastia and breast tenderness are uncommon side effects. Also, there have been some associations with supplementation and the development or exacerbation of sleep apnea.[41]

Conclusions

Androgen deficiency in the aging male (ADAM) describes a common clinical condition that may affect many elderly men and is likely under diagnosed because of the vague clinical symptoms. It is apparent that testosterone supplementation may improve many of the most common symptoms including bone density, body composition, mood and cognition, and sexual function. Supplementation is not without risks which are primarily associated with prostate events. However, evidence suggests that there is no correlation with supplementation and exacerbation of BPH or development of prostate cancer over the general population. Proper monitoring is necessary however. Recommendations include digital rectal exam, PSA, blood count, and liver function tests prior to initiation of therapy. During therapy, periodic digital rectal exam, PSA, and blood counts should be closely monitored.

Disclosure

Dr. Cully Carson is a member of the Speakers' Bureau for Auxilium Pharmaceuticcals, Pfizer and Lilly. He is a consultant for Pfizer and Lilly. □

References

1. Korenman SG et al. Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab* 1990;71(4):963-969.
2. Morales A, Heaton JP, Carson CC 3rd. Andropause: a misnomer for a true clinical entity. *J Urol* 2000;163(3):705-712.
3. Araujo AB et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007 [Epub ahead of print]
4. United States Census Bureau. 2005.
5. Harman SM et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2001;86(2):724-731.
6. Morley JE et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 1997;46(4):410-413.
7. Herbert J. The age of dehydroepiandrosterone. *Lancet* 1995;345(8959):1193-1194.
8. Compston JE. Sex steroids and bone. *Physiol Rev* 2001;81(1):419-447.
9. Slemenda, CW et al. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. *J Clin Invest* 1997;100(7):1755-1759.
10. van den Beld AW et al. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 2000;85(9):3276-3282.
11. Michael H et al. *Estrogen and testosterone use different cellular pathways to inhibit osteoclastogenesis and bone resorption*. *J Bone Miner Res* 2005;20(12):2224-2232.
12. Fink HA et al. Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab* 2006;91(10):3908-3915.
13. Holzbeierlein JM, McLaughlin MD, Thrasher JB. Complications of androgen deprivation therapy for prostate cancer. *Curr Opin Urol* 2004;14(3):177-183.
14. Isidori AM 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.
15. Hijazi RA, Cunningham GR. Andropause: is androgen replacement therapy indicated for the aging male? *Annu Rev Med* 2005;56:117-137.
16. Moffat SD et al. 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.
17. Moffat SD et al. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004;62(2):188-193.
18. Rosario ER et al. Age-related testosterone depletion and the development of Alzheimer disease. *JAMA* 2004;292(12):1431-1432.
19. Ramsden M et al. Androgens modulate beta-amyloid levels in male rat brain. *J Neurochem* 2003;87(4):1052-1055.
20. Ramsden M, Shin TM, Pike CJ. Androgens modulate neuronal vulnerability to kainate lesion. *Neuroscience* 2003;122(3):573-578.
21. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. *Eur J Endocrinol* 2006;155(6):773-781.
22. Seidman SN et al. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry* 2001;62(6):406-412.
23. Pope HG Jr et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003;160(1):105-111.
24. Bhasin S. Regulation of body composition by androgens. *J Endocrinol Invest* 2003;26(9):814-822.
25. Mauras N et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab* 1998;83(6):1886-1892.
26. Snyder PJ et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(8):2647-2653.
27. Blackman MR et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 2002;288(18):2282-2292.
28. Giannoulis MG et al. The Effects of Growth Hormone and/or Testosterone in Healthy Elderly Men: A Randomized Controlled Trial. *J Clin Endocrinol Metab* 2005.

29. Bhasin S et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996;335(1):1-7.
30. Wang C. 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.
31. Woodhouse LJ et al. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J Clin Endocrinol Metab* 2004;89(2):718-726.
32. Carani C et al. The effects of testosterone replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men. *Psychoneuroendocrinology* 1995;20(7):743-753.
33. Skakkebaek NE et al. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol (Oxf)* 1981;14(1):49-61.
34. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000;164(2):371-375.
35. Isidori AM et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(4):381-394.
36. Mulhall JP et al. Effect of testosterone supplementation on sexual function in hypogonadal men with erectile dysfunction. *Urology* 2004;63(2):348-352;discussion 352-353.
37. Shabsigh R et al. 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.
38. Morales A et al. Testosterone supplementation for hypogonadal impotence: assessment of biochemical measures and therapeutic outcomes. *J Urol* 1997;157(3):849-854.
39. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996;334(11):707-714.
40. Hajjar RR, Kaiser FE, Morley JE Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab* 1997;82(11):3793-3796.
41. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004;350(5):482-492.
42. Calof OM 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.
43. Kabakci G et al. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. *Cardiology* 1999;92(4):221-225.
44. English KM et al. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J* 2000;21(11):890-894.
45. Hak AE et al. 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.
46. Whitsel EA et al. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med* 2001;111(4):261-269.
47. Morales A. Androgen replacement therapy and prostate safety. *Eur Urol* 2002;41(2):113-120.
48. Meikle AW et al. Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. *Urology* 1997;49(2):191-196.
49. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf)* 1994;40(3):341-349.
50. Rhoden EL, MorgentalerA. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003:170(6 Pt 1):2348-2351.
51. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 2004;172(3):920-922.
52. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 2005;173(2):533-536.