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Review

Managing the Risks of Prostate Disease During Testosterone Replacement Therapy in Older Men: Recommendations for a Standardized Monitoring Plan

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Growing Use of Androgenic Products

The powerful demographic trend toward aging of populations in most countries has appropriately focused attention on the health problems of older men. Although there is agreement that serum total, bioavailable, and free testosterone concentrations decline with advancing age (Haffner et al, 1996; Kaufman and Vermeulen 1997; Morley et al, 1997; Zmuda et al, 1997; Smith et al, 2000; Harman et al, 2001), there is considerable uncertainty about the benefits and risks of testosterone replacement in older men with low testosterone concentrations (Bhasin and Buckwalter 2001; Matsumoto 2002). Initial randomized, placebo-controlled studies (Tenover 1992, 1998; Morley et al, 1993; Sih et al, 1997; Snyder et al, 1999a,b; Urban 1999; Kenny et al, 2001) have established the feasibility of testosterone replacement in older men for up to 3 years, and demonstrated that testosterone replacement increases fat-free mass, sense of well-being, and bone mineral density, and decreases fat mass in older men with low or low-normal testosterone concentrations. However, these initial studies (Tenover 1992, 1998; Morley et al, 1993; Sih et al, 1997; Snyder et al, 1999a,b; Urban 1999; Kenny et al, 2001) were neither designed to determine the effects of testosterone supplementation on health outcomes such as fracture rates, falls, physical function, disability, neurocognitive ability, and progression to dementia, nor powered to evaluate the effects of androgen administration on prostate and cardiovascular event rates. Long-term studies of 1 to 3 years in duration (Sih et al, 1997; Tenover 1998; Snyder et al, 1999a,b; Kenny et al, 2001) have generally reported a greater increase in hematocrit with testosterone administration than that associated with placebo

administration. A few older men will develop hematocrits >55% during testosterone administration; increases in hematocrit to these high levels would increase blood viscosity, decrease blood flow rates, and might increase the risk of stroke. Androgen replacement may also worsen or induce sleep apnea, and cause edema, especially in older men with pre-existing heart disease.

In the context of this uncertainty about the long-term risks of testosterone supplementation in older men, it is notable that testosterone prescription sales have increased 1700% in the last 9 years, and have grown 460% just in the last 3 years. Testosterone sales that had been stagnant at about $18 million until 1988 are projected to reach $400 million before the end of 2002 (IMS sales data, Philadelphia, Pa; BMC Corporation sales data, Minne-apolis, Minn). Whereas the greatest growth in testosterone sales appears to be in men with hypogonadism and younger than 65 years of age, testosterone use is also growing in older men. A growing interest in testosterone use is reflected in greater media and public attention that this topic has received.

Although prostate event rates have not been significantly different between placebo- and testosterone-treated men in the previously published studies of testosterone replacement in older men (Sih et al, 1997; Tenover 1998; Snyder et al, 1999a,b), it is important to recognize that these studies did not have sufficient power to detect significant differences in prostate event rates between the 2 groups. It has been estimated that in order to detect a 30% difference in prostate cancer incidence rates between the placebo- and testosterone-treated groups, it would require randomization of approximately 6000 older men with low testosterone levels to the placebo and testosterone groups and treatment for an average of 5 years. Because such a randomized clinical trial would likely include relatively healthy older men with unequivocally low testosterone levels who do not have prostate cancer or prostate-specific antigen (PSA) levels >4 ng/mL, this would require screening a significantly larger number of older men in order to enroll 6000 eligible men. Accrual of sufficient numbers of men in such a clinical trial would be a challenging task. At this time, no study of this size has been funded; therefore, we will not know for several years whether testosterone replacement increases the incidence of clinically overt prostate cancer.

Because the baseline prevalence of benign as well as malignant prostatic disorders is high (Berry et al, 1984; Carter et al, 1990; Sakr et al, 1994; Coley et al, 1995; Hsing et al, 2000; Jemal et al, 2002) in older men and the risks of prostate problems during testosterone administration remain undefined, there is understandable anxiety among health care providers who are facing increasing pressure from patients to consider hormone replacement. Therefore, the objectives of this commentary are to review the available data on the effects of testosterone replacement on the risk of prostatic disease in older men, and to present some recommendations for prostate monitoring during androgen administration in older men.

This review should not be construed as our endorsement of testosterone replacement in older men with low testosterone concentrations. Our position is that at present, insufficient data exist to warrant a general recommendation for testosterone replacement of all older men with low testosterone concentrations, but that in some patients with unequivocally low testosterone levels and clinical and laboratory findings that can be attributed to androgen deficiency, individualized testosterone replacement might be justified after appropriate discussion of the benefits and risks with the patient, and institution of a standardized monitoring plan to maximize patient safety and minimize risk.

Issues Associated With Prostate Risks and Monitoring in Older Men

Most but not all authorities believe that testosterone does not cause prostate cancer. Also, there is no consistent relationship between endogenous serum testosterone levels and the risk of prostate

cancer. However, there are a number of areas of concern.

1. Prostate cancer is a common, androgen–dependent tumor, and androgen administration promotes tumor growth in patients with metastatic prostate cancer (Fowler and Whitmore 1981; Manni et al, 1988; Santen et al, 1990). Therefore, testosterone administration is absolutely contraindicated in men with a clinical prostate cancer.
2. PSA levels increase with age in men who do not have clinical prostate cancer (Oesterling et al, 1993), and levels are higher in blacks than in whites (Morgan et al, 1996).
3. Some men with PSA <4.0 ng/mL will have or will develop clinical prostate cancer. The risk of developing a clinical prostate cancer is related to the baseline PSA value (Gann et al, 1995; Fang et al, 2001).
4. Many older men have occult, microscopic foci of cancer in their prostates (Guileyardo et al, 1980; Carter et al, 1990; Sakr et al, 1994). We do not know whether testosterone administration will make these subclinical foci of cancer grow and become clinically overt.
5. Older men with low testosterone levels may have occult or clinical prostate cancer (Morgentaler, 1996; Schatzl et al, 2001). Because PSA levels may be lower in men with androgen deficiency than in men with eugonadism, PSA levels in men with low testosterone levels may not accurately reflect the presence of prostate cancer.
6. Serum PSA levels may be lower in men with testosterone deficiency and are restored to levels seen in age-matched controls following testosterone replacement (Sasagawa, 1990; Behre, 1994; Cooper et al, 1996; Meikle et al, 1997; Svetec et al, 1997). Therefore, in men receiving testosterone replacement, it is important to determine whether the increments in PSA levels are greater than what is expected after testosterone administration in men without prostate cancer. Increased PSA levels can be caused by prostatitis, assay variability, differences between PSA assays, biological variability, testosterone replacement, benign prostatic hyperplasia (BPH), as well as prostate cancer. When PSA levels in men with androgen deficiency and a testosterone replacement regimen show a change from baseline or from a previously measured value, the clinician must consider each of these factors before suggesting that the patient undergo prostate biopsies.
7. More intensive PSA screening and follow-up of men receiving testosterone replacement might lead to greater numbers of prostate biopsies and detection of subclinical prostate cancers that would have otherwise remained undetected. Therefore, it is important to set criteria for monitoring PSA changes during testosterone supplementation. Criteria that use very low thresholds for performing prostate biopsy relative to test-retest variability will likely result in an excessive number of biopsies with their associated costs, psychological trauma, and morbidity. On the other hand, criteria that use unreasonably high thresholds for performing prostate biopsies may fail to detect clinical prostate cancers at an early stage.

Testosterone and Prostate Cancer Risk

Many Clinically Overt Prostate Cancers are Androgen-Responsive—Pioneering observations by Huggins (1941) demonstrated that many metastatic prostate cancers regress after surgical orchiectomy. Since then, androgen ablation has been shown to induce temporary remission in approximately 80% of patients with metastatic prostate cancer, and has become a widely used treatment modality for this common disorder (Denis 1989; Neri et al, 1989; Beland et al, 1990; Schmitt et al, 2000). Suppression of testosterone concentrations, or action by surgical castration, or by administration of a gonatotropin-receptor hormone (GnRH) agonist, GnRH antagonist, antiandrogen, or estrogen is determined the basis of hormonal therapy of metastatic prostate cancer. Conversely, a study (Fowler and Whitmore 1981) of patients with metastatic prostate cancer documented tumor progression in 33 of 34 patients who received testosterone supplementation, and whose disease had relapsed prior to

testosterone treatment. Thus, androgen ablation initially causes a remission in most men with prostrate cancer, and androgen supplementation causes metastatic prostate cancer to flare.

The Effect of Testosterone Supplementation on the Course of Subclinical Prostate Cancers Is Unknown— Many aging men with normal serum levels of testosterone will have occult prostate cancers that never become clinical prostate cancers (Guileyardo et al, 1980; Carter et al, 1990; Sakr et al, 1994). The percentage of men with occult prostate cancers at autopsy increases with age and is >50% in the latter decades of life. The prevalence of occult prostate cancer is similar in American and Japanese men living in Japan (Carter et al, 1990). However, the incidence of clinical prostate cancer was 137.0 and 100.8 per 100 000 in American blacks and whites, respectively, and 9.0 per 100 000 in Japanese men living in Japan (Hsing and Devesa 2001). Available data do not indicate a significant difference in serum levels of testosterone among older men of different ethnic groups. It has been hypothesized that greater transcriptional activity of androgen receptor due to polymorphisms of the polyglutamine tract length in exon 1 of the receptor protein (Hardy et al, 1996; Giovannucci et al, 1997; Menin et al, 2001), or amplification of androgen action because of polymorphisms of the steroid 5 alpha-reductase (SRD5A2) locus (Margiotti et al, 2000; Hsing et al, 2001), which encodes the human prostatic (or type II) steroid 5 alpha-reductase enzyme, might contribute to some of the increased risk of prostate cancer in some high-risk groups.

Mortality due to prostate cancer varies inversely with age (Gatling, 1990), and most occult prostate cancers do not become clinical prostate cancers. Many of the occult cancers must occur in eugonadal men, however, it is not known whether the androgen deficiency that is associated with aging reduces the risk of an occult prostate cancer becoming a clinical prostate cancer. It is possible that testosterone administration might cause these latent or occult prostate cancers to grow and become clinically significant prostate cancer. Currently, we do not know the long-term effects of testosterone replacement on occult prostate cancers.

In prospective, randomized controlled trials and retrospective reviews of clinical experience (Tenover 1992, 1998; Morley et al, 1993; Sih et al, 1997; Snyder et al, 1999a,b; Kenny et al, 2001), the total number of prostate cancers has not been numerically greater in testosterone-treated men than in placebo-treated men. However, all of the published studies (Tenover 1992, 1998; Morley et al, 1993; Sih et al, 1997; Snyder et al, 1999a,b; Kenny et al, 2001) have collectively treated fewer than 500 carefully selected, older men who had been rigorously screened for prostate cancer prior to treatment and meticulously followed. It will require a large clinical trial to assess the frequency with which testosterone supplementation might increase the frequency of clinically overt prostate cancers. For instance, to detect a 30% difference in the incidence rates of prostate cancers between testosterone-treated and placebo-treated men, approximately 6000 older men, 65–80 years of age, with low testosterone levels, will need to be randomized to each of the 2 treatment groups (placebo and testosterone). Assuming a 1.2% yearly incidence rate of newly diagnosed prostate cancers in men of this age group (Landis et al, 1998; Landis et al, 1999; Greenlee et al, 2000), the average treatment duration will have to be 5 years. A study of this magnitude, duration, and complexity would inevitably require allocation of substantial resources and infrastructure, but one is sorely needed to answer this crucial question about the safety of testosterone administration in older men.

Epidemiological Data on the Relationship Between Serum Testosterone Levels and Prostate Cancer

Epidemiological studies have failed to demonstrate a consistent, dose-related correlation between prostate cancer risk and sex hormone levels (Jackson et al, 1977, 1981; Ahluwalia et al, 1981; Meikle and Stanish 1982; Zumoff et al, 1982; Hulka et al, 1987; Nomura et al, 1988; Meikle et al, 1989; Barrett-Connor et al, 1990; Andersson et al, 1993; Hsing and Comstock 1993; Gann et al, 1996;

Nomura et al, 1996; Demark-Wahnefried et al, 1997; Guess et al, 1997; Vatten et al, 1997; Wolk et al, 1997; Dorgan et al, 1998; Heikkila et al, 1999; Hawk et al, 2000; Shaneyfelt et al, 2000; Mohr et al, 2001; Slater, 2000). A majority of case-control studies have found no significant association between serum testosterone or dihydrotestosterone (DHT) concentrations and the risk of prostate cancer. Eaton and colleagues (1999) reported a quantitative review of the data from 8 prospective epidemiological studies and concluded that there are no large differences in circulating hormones between men who subsequently go on to develop prostate cancer and those who remain free of the disease. In a meta-analysis of 28 case control studies by Shaneyfelt et al (2000), 17 showed no difference between serum testosterone levels between men with prostate cancer and controls, 6 had lower testosterone levels, and only 6 showed higher levels. Remarkably, in 2 cohort and nested-case control studies (Nomura et al, 1988; Hsing and Comstock 1993; Gann et al, 1996), men with the higher quartile of serum testosterone concentrations, after adjustment for age, body mass index, DHT and estradiol, had 2.3 times the risk for prostate cancer than men in the lowest quartile. The increased risk is largely attributed to one study (Gann et al, 1996) in which low sex hormone-binding globulin (SHBG) levels were correlated with high serum testosterone levels, an unusual finding that is not reported in any other study. It also should be mentioned that 2 large, prospective, longitudinal studies of middle-aged and older men—the Rancho Bernardo Study—(Barrett-Connor et al, 1990) and the Massachusetts Male Aging Study (Mohr et al, 2001)—did not find a significant association or a dose-response relation between serum testosterone concentrations and the risk of prostate cancer.

None of the studies that measured DHT and estradiol found higher levels of these hormones in cases than in controls. SHBG levels have also not been significantly different between cases and controls in a majority of studies with the exception of one study (Gann et al, 1996).

Thus, the available evidence is conflicting and inconclusive on whether high testosterone concentrations confer a higher risk of prostate cancer in men. In many studies, the hormone measurements were performed on single, stored samples that were collected at different times of the day, which may have introduced a bias. The interpretation of data from epidemiological studies is confounded also by the variability in study design and methods for hormone measurements. The criteria used for selecting controls varied considerably and were not optimal in some studies. Many of the studies did not take into account the effects of prostate cancer and other concomitant illnesses on hormone levels, particularly in older men, and the high correlation between circulating concentrations of testosterone, estradiol, DHT, and SHBG. Finally, analyses of serum hormone levels does not take into account the possibility that circulating concentrations of hormones might not accurately reflect hormone action or concentrations at the tissue level, particularly within the prostate. An ongoing randomized, double-blind study of finasteride for the prevention of prostate cancer may provide important insights into the role of intraprostatic and circulating DHT concentrations in the pathophysiolgy of prostate cancer.

The problems inherent in epidemiological association studies have been highlighted recently by the firestorm that erupted after the release of data from the Women's Health Initiative on the effects of estrogen. The data from this and other randomized, controlled, intervention trials have contrasted sharply with the data from previous epidemiological studies that had reported lower cardiovascular mortality in estrogen users. The results of the Women's Health Initiative (2002) and the HERS (Hulley et al, 1998) emphasize the need for definitive, randomized, placebo-controlled studies of testosterone supplementation in older men.

Biopsy-Diagnosed Prostate Cancer in Men with Low Testosterone Levels

Morgentaler et al (1996) evaluated 77 men with low total testosterone or free testosterone (measured by a tracer analogue assay) concentrations. These men with a mean age of 58 years had a normal

digital rectal examination of the prostate, a PSA level of ≤4.0 ng/mL, and underwent sextant biopsies of the prostate. Eleven of 77 men (14%) were found to have prostate cancer with Gleason scores of 6 or 7. Serum PSA concentrations, PSA density, prostate volume, and total or free testosterone concentrations were not significantly different between men who had cancer and those who did not. This study did not have a control group, and we do not know whether sextant biopsies of age-matched controls with normal testosterone levels would yield a similarly high incidence of biopsy-detectable cancer. In another study of 332 men whose mean age was 64.2 years and who had PSA levels 2.6 to 4.0 ng/mL and a benign prostate examination, cancer was found in 22% of the biopsies (Catalona et al, 1997). In 2 additional studies, positive biopsies were found in 24% of 273 (Djavan et al, 1999) and 24% of 151 men (Babaian et al, 2001) with PSA levels between 2.5 and 4.0 ng/mL and a normal digital examination of the prostate. Therefore, the study by Morgenthaler et al (1996) should not be interpreted to indicate that there is an increased prevalence of latent prostate cancer in men with low free or total testosterone levels, or that prostate biopsies are needed in all men with low testosterone concentrations.

Two reports found a higher prevalence of prostate cancer in the biopsies and a higher histological prostate cancer score in men with low testosterone levels (Hoffman et al, 2000; Schatzl et al, 2001). Hoffman and colleagues (2000) evaluated 117 consecutive patients diagnosed with prostate cancer; 57 of these 117 men subsequently underwent radical prostatectomy. Men with low testosterone levels were older (69 vs 61.9 years), had a higher percentage of biopsies that revealed cancer (43% vs 22%, $P < .01$), and had a higher percentage of biopsies with a Gleason score of 8 or greater (7 of 64 vs 0 of 48, $P < .025$). Another study (Schatzl et al, 2001) reported that in men with prostate cancer, low testosterone levels are associated with somewhat higher-grade prostate cancers than in men with normal testosterone levels even though age, PSA level, and prostate volume were similar in the men with low and normal testosterone levels. These studies selected men who were diagnosed with prostate cancer and then analyzed the tumor characteristics on the basis of patients' serum levels of testosterone. Lack of appropriate controls that are matched for nutritional state and body composition makes it difficult to interpret these data. These data emphasize the need to be vigilant about the risk of prostate cancer even in men with low testosterone levels; however, these data should not be interpreted to indicate that low testosterone levels are a risk factor for prostate cancer.

Interpreting Changes in Serum PSA Levels During Testosterone Replacement Therapy

Data from Intervention Studies of Testosterone Replacement in Young and Older Men With Hypogonadism— Lowering of serum testosterone concentrations by withdrawal of androgen therapy in young men with hypogonadism is associated with a decrease in serum PSA levels (Meikle, 1997). Similarly, treatment of men with BPH with a 5-alpha reductase inhibitor, finasteride, is associated with a significant lowering of serum and prostatic PSA levels (Gormley et al, 1992).

Conversely, several studies (Holmang et al, 1993; Behre and Nieschlag, 1994; Gooren 1994; Douglas et al, 1995; Arver et al, 1997; Meikle et al, 1997; Ozata et al, 1997; Svetec et al, 1997; Bhasin et al, 1998; Wang et al, 2000; Jin et al, 2001; Shibasaki et al, 2001; Singh et al, 2001; Hong and Ahn 2002) of testosterone replacement in healthy young men with hypogonadism have demonstrated a significant increase in serum PSA levels after testosterone administration (Table 1), although some studies have reported no significant change in PSA levels (Cooper et al, 1996; Katznelson et al, 1996; Snyder et al, 2000). In a systematic review of published studies of testosterone replacement in men with hypogonadism, we have calculated the weighted effect size to be 0.68 standard deviation units with a 95% confidence interval of 0.55 to 0.82, which is statistically significant. This means that the average effect of testosterone replacement therapy is to increase PSA levels by about 0.68 standard deviations over baseline. Because the average standard deviation was 0.47 in this

systematic analysis, the standard deviation score of 0.68 translates into an average increase in serum PSA levels of about 0.30 ng/mL. There is considerable variability in the magnitude of change in PSA after testosterone supplementation among these studies ($P < .00001$), in part due to the heterogeneity of study populations, inclusion of older men in some studies but not others, and differences in PSA assays. In addition, many patients who were enrolled in these studies were likely receiving testosterone replacement therapy previously; we do not know whether the washout period was sufficient to revert PSA levels to baseline. Therefore, it is possible that because of inadequate washout, the increments in serum PSA levels after testosterone administration might have been underestimated.

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Table 1. *Change in serum PSA concentrations in healthy, hypogonadal men after testosterone replacement therapy* *

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Table 2. *Change in serum PSA concentrations in older men with low or low-normal testosterone concentrations* *

To evaluate whether older men experience a greater increase in PSA after testosterone supplementation, we performed a separate systematic review of data from placebo-controlled trials of testosterone supplementation in older men with low or low-normal testosterone concentrations (Tenover 1992; Morley et al, 1993; Urban et al, 1995; Sih et al, 1997; Snyder et al, 1999a; Kenny et al, 2001). The weighted effect size in 6 studies of older men was 1.48 standard deviation units, with a 95% confidence interval of 1.21 to 1.75, which was statistically significant. Thus, on average, older men experience a greater increase in serum PSA concentrations than populations of predominantly younger men. The average effect of testosterone replacement in older men is to increase PSA levels by almost 1.5 standard deviations over baseline. There is, however, significant variability in the results among these 6 studies ($P < .0001$), and the average standard deviation was skewed by 1 study, which had a very high standard deviation (Kenny et al, 2001). After excluding this study, the average change in serum PSA levels after testosterone replacement in studies of older men was 0.43 ng/mL.

In the long-term, randomized, placebo-controlled trials of testosterone supplementation in older men (Sih et al, 1997; Snyder et al, 1999a,b; Kenny et al, 2001), the changes in PSA levels in testosterone-treated men were not significantly different from that in placebo-treated men (Table 2). Two short-term clinical trials of testosterone supplementation in older men (Tenover 1992; Urban 1999) did report statistically significant increments in PSA levels after testosterone treatment, although the increments in PSA levels were modest; serum PSA level increased from 2.1 to 2.7 ng/mL in one trial (Tenover 1992), and from 1.7 to 2.1 ng/mL in the other trial (Urban 1999).

In young men with eugonadism, administration of supraphysiological doses of testosterone does not further increase serum PSA levels (Bhasin et al, 1996; Wu et al, 1996). These data are consistent with dose-response studies in young men (Bhasin et al, 2001) that demonstrate that maximal serum concentrations of PSA are achieved at testosterone levels that are at the lower end of the normal

male range; higher testosterone concentrations are not associated with higher PSA levels.

These data taken together suggest that the administration of replacement doses of testosterone in men with androgen deficiency can be expected to produce a modest increment in serum PSA levels. Increments in PSA levels after testosterone supplementation in men with androgen deficiency are generally less than 0.5 ng/mL, and increments in excess of 1.0 ng/mL over a 3–6 month period are unusual. Nevertheless, administration of testosterone to men with baseline PSA levels between 2.5 and 4.0 ng/mL will cause PSA levels to exceed 4.0 ng/mL in some men. Increments in PSA levels above 4 ng/mL will trigger a urological consultation and many of these men will be asked to undergo prostate biopsies.

Variation in PSA Concentrations Due To Assay Variability and Aging-Related Change— There is considerable test-retest variability in PSA measurements. Some of this variability is due to the inherent assay variability, and a significant portion of this variability is due to unknown factors. Kadmon and colleagues (1996) determined the variability of serum PSA levels in men without prostate cancer. The interassay coefficient of variation was 7.5%. Fluctuations in serum PSA occurred in 78% of the men over a 2-year follow up period, and 12.5% had at least a single PSA increase exceeding 0.75 ng/mL per year. Fluctuations were larger with higher mean PSA levels. There is some evidence that the interassay variation is greater than 1 ng/mL in a significant percentage of samples assayed with the Hybritech assay (Manseck et al, 1998). Interassay variability is reported to be less with the Abbott Asym assay. Variability can be even greater if measurements are performed in different laboratories that use dissimilar assay methodologies (Riehmann et al, 1993; Wenzl et al, 1998). The 95% confidence limits for the change in PSA levels between 2 tests performed 3–6 months apart in the placebo-treated men in a study of finasteride in men with BPH was 1.4 ng/mL or 49% of baseline value (Gormley et al, 1992); therefore, a change of >1.4 ng/mL in samples drawn 3–6 months apart has been used as a criterion for seeking urological evaluation in some clinical trials of finasteride (McConnell et al, 1998). As a rough approximation, the interassay coefficient of variation of PSA assays on average has been reported to be 15% (Ornstein et al, 1997). The coefficient of variation of the PSA assay should be taken into account when evaluating the change in PSA between samples drawn at different times or when interpreting the PSA velocity (see *PSA Velocity Criteria* in section later).

Some types of prostatic manipulations such as prostatic massage, needle biopsy, and transurethral retrograde prostatectomy (TURP) can significantly increase PSA levels, whereas other procedures such as digital rectal examination, cystoscopy, and ejaculation have very little effect on serum PSA levels (Klein and Lowe 1997). These factors should be considered in the interpretation of elevated PSA levels.

Application of the PSA Velocity Criterion to Prostate Monitoring During Testosterone Administration— In patients in whom sequential PSA measurements are available for more than 2 years, Carter and Pearson (1993) have proposed the use of PSA velocity criterion to identify men at higher risk for prostate cancer. A PSA velocity criterion has not been used in any of the published clinical trials of testosterone supplementation. Based on the analysis of the data of men in the Baltimore Longitudinal Study of Aging, Carter et al (1995) demonstrated that if the baseline PSA were between 4 and 10 ng/mL, a rate of change of >0.75 ng/mL/y in PSA was unusual in men with benign prostatic disease. Because most men receiving testosterone replacement will have baseline PSA levels <4.0 ng/mL, the criteria established for baseline PSA values between 4 and 10 ng/mL are too lenient. In a recent analysis of data from the Baltimore Longitudinal Aging Study, Fang et al (2002) reported the PSA velocity in men with prostate cancers who have baseline PSA <4 ng/mL. In these men with initial PSA of less than 4 ng/mL, the long-term follow-up indicated that a cut point for PSA

velocity of 0.1 ng/mL per year had a sensitivity of 81% and a specificity of 50% for the detection of prostate cancer. Setting the threshold at 0.2 ng/mL per year gave a sensitivity of 52.4% and a specificity of 79.4%. These findings need to be confirmed; however, it should be recognized that in view of the considerable test-retest variability in PSA levels in the same individual, setting thresholds for prostate biopsy that are substantially lower than the test-retest variability would likely result in a large number of false triggers for biopsy.

The use of PSA velocity criterion is likely to be more useful in men in whom PSA data are available over many years so that the PSA change over baseline exceeds the expected interassay variability. As an illustration, consider the case of a man with baseline PSA of 2.4 ng/mL and whose PSA after 2 years of testosterone supplementation is 3 ng/mL. The absolute 2-year change in PSA of 0.6 ng/mL translates into a PSA velocity of 0.3 ng/mL/y, and exceeds the threshold of 0.2 ng/mL/y proposed by Fang et al (2002). However, because this change of 0.6 ng/mL is less than 2 times the interassay CV (30% or 0.72 ng/mL), it should be viewed with caution and followed by closer follow-up of PSA values over the subsequent year rather than immediate prostate biopsy. It should be emphasized that the study by Fang et al (2002) involved a relatively small number of men who developed prostate cancer over a long period (10 years) of follow up. In another study a PSA velocity cutoff of 0.75 ng/mL or more per year provided a sensitivity of 79% and a specificity of 66% in predicting prostate cancer (Smith and Catalona 1994). These observations came from a prostate cancer detection study that involved 312 men with baseline PSA levels of <4.0 ng/mL and who subsequently developed PSA values >4.0 ng/mL. All men with verified PSA levels >4.0 ng/mL underwent prostate biopsies. Follow-up was for up to 5 years.

Carter and Pearson (1993) have emphasized that PSA velocity should not be used for follow-up periods of less than 2 years. Also, estimation of PSA velocity requires multiple PSA measurements over time. PSA velocity is calculated as the total change in PSA from baseline divided by the time in years. A PSA velocity of >0.2 ng/mL/y does not imply that the patient has prostate cancer, nor should it be used to dictate immediate prostate biopsy; rather, it signifies a higher than average risk for developing prostate cancer during the subsequent decades Therefore, PSA velocity can be particularly useful during long-term follow-up of patients over many years. For periods of less than 3 years, we propose that PSA velocity of >0.4 ng/mL/y should warrant a urological evaluation and more intensive future surveillance for prostate cancer. For follow-up periods exceeding 3 years, a PSA velocity of >0.2 ng/mL/y is likely associated with a greater than average risk of prostate cancer and should warrant a closer follow-up of the patient. Neither of these PSA velocity criteria that we have proposed has been tested for specificity or sensitivity in prospective trials of testosterone replacement; they should be viewed as the authors' opinions based on a relatively limited amount of data.

Effects of Testosterone Supplementation on Prostate Volume and Course of BPH— Prostate size increases during the pubertal years; after completion of pubertal growth, there is little change in prostate size until approximately 50 years of age. After 50 years of age, prostate size begins to increase again (Berry et al, 1984). Histological BPH is uncommon in men in their 30s and 40s, and its prevalence increases with age so that by age 80, about 80% of men have histological evidence of BPH. About half of these men develop macronodular BPH. There is no clear correlation between serum androgen concentrations and prostate size in men. As men age, the prostate volume increases, whereas serum total and free testosterone concentrations decrease. Most but not all studies have found that mean serum DHT and estradiol levels remain relatively constant in men with advancing age. There is, however, a correlation between prostate volume and PSA. The PLESS study showed that baseline PSA and prostate volume are powerful predictors of the risk of acute urinary retention and the need for BPH-related surgery (Roehrborn et al, 2000).

Lowering of serum testosterone concentrations by administration of a GnRH agonist, or blocking androgen effects by administration of an antiandrogen is associated with a reduction in prostate volume. These treatments are typically associated with a 20%–30% reduction in prostate volume. Inhibition of steroid 5-alpha-reductase enzyme by finasteride decreases serum and intraprostatic DHT concentration, and was associated with an average 16% reduction in prostate volume in a large multicenter study (Gormley et al, 1992). Thus, once established, androgen deprivation is moderately effective in reducing prostate volume.

In young men with hypogonadism, prostate volumes are lower than in age-matched controls, and testosterone replacement therapy increases prostate volume to that of age-matched controls (Behre, 1994; Meikle, 1997). However, continued treatment with replacement doses of testosterone does not increase prostate volume progressively or above the size expected for age. Treatment of BPH usually is guided by the severity of symptoms, and prostate volume and symptoms usually are not closely correlated. In placebo-controlled, randomized, clinical trials of testosterone in older men with low or low-normal testosterone levels (Sih et al, 1997; Tenover 1998; Snyder et al, 1999a,b), there were no significant differences in the frequency of prostate events or invasive procedures between placebo and testosterone-treated men. Although 2 of the randomized clinical trials were of 3 years duration (Tenover 1998; Snyder et al, 1999a,b), none of the previous studies was powered to detect clinically meaningful differences in prostate event rates. They did not involve a large enough number of men for a long enough time to answer this issue. Therefore, we do not know whether testosterone replacement therapy will increase the need for invasive treatment of BPH.

Testosterone replacement can be administered safely to men with BPH who have mild to moderate symptom scores (Table 4). The severity of symptoms associated with BPH can be assessed by using either the International Prostate Symptom Score (IPSS) or the American Urological Association (AUA) Symptom questionnaires. Because androgen replacement in men with androgen deficiency increases prostate volumes only modestly (Sasagawa, 1990; Behre, 1994; Cooper et al, 1996; Meikle, 1997), there is typically little or no change in prostate symptom scores in most men treated with replacement doses of testosterone. However, it is possible that in patients with pre-existing, severe symptoms of BPH, even small increases in prostate volume during testosterone administration may exacerbate obstructive symptoms. In these men, testosterone should either not be administered or it should be administered with careful monitoring of their obstructive symptoms and only after their prostatic enlargement has been effectively treated urologically.

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Table 4. *Prostatic disorders that constitute relative or absolute contraindications for androgen supplementation*

Use of Other Prostate Markers for Monitoring— The utility of measurements of free and complexed PSA for prostate cancer screening has been investigated in several trials (Polascik et al, 1999; Djavan et al, 2002; Ellison et al, 2002); these studies generally suggest that percent free PSA improves the specificity for prostate cancer detection in men with PSA values between 4 and 10 ng/mL. However, these studies have not demonstrated higher predictive value with the use of algorithms that employ digital rectal examination, total PSA, and the ratio of free to total PSA over algorithms that use only digital rectal examination and total PSA. The cost:benefit analyses have yet to establish the utility of using free to total PSA ratio or complexed PSA in population

screening for prostate cancer.

Some studies have suggested that a PSA density of greater than 0.15 may better distinguish BPH from prostate cancer (Polascik, 1999) than PSA alone; the predictive value and cost effectiveness of such as an approach for population screening of older men has not been evaluated in large, prospective, clinical trials. The calculation of PSA density requires the measurement of prostate volume by the use of ultrasound; this adds significantly to the cost of screening. In addition, no data are currently available from testosterone trials to rationalize the use of either free to total PSA ratio or PSA density in prostate screening during testosterone supplementation.

Monitoring Recommendations

Monitoring PSA Levels in Older Men Receiving Testosterone Replacement— Older men considering testosterone supplementation should undergo digital examination of the prostate, evaluation of risk factors for prostate cancer, and symptom scores for BPH using either the AUA or the IPSS questionnaire, and a baseline PSA measurement (Table 3). As a general rule, men with a previous history of prostate cancer should not be given androgen supplementation, and those with palpable abnormalities of the prostate or PSA levels >4 ng/mL should undergo urological evaluation (Table 4). We recognize that some men with hypogonadism who have had a radical prostatectomy for prostate cancer and undetectable PSA levels for several years may be "cured" and may be candidates for testosterone replacement therapy. Because testosterone administration could potentially promote the growth of residual cancer, replacement therapy in this setting should only be considered after urological consultation and after a thorough discussion of the potential risks. If replacement therapy is provided to such men, PSA levels must be monitored more frequently. Men with BPH and mild to moderate symptoms of (AUA symptom score less than 21) can be safely treated with testosterone replacement with careful follow-up.

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Table 3. *Recommendations for monitoring prostate-related, adverse experiences during testosterone replacement in older men*

After initiation of testosterone replacement therapy, PSA levels and digital examination of the prostate should be repeated at 3, 6, and 12 months, and annually thereafter (Andropause Consensus Panel, 2001). Clinical experience and data from controlled clinical trials have established that the increments in PSA levels after testosterone administration in men with hypogonadism occur in the first 3–6 months, at which point new steady state PSA levels are achieved. Continued treatment beyond 12–24-weeks would be expected to be associated only with predictable, age-related changes in PSA levels. Therefore, excessive increases in serum PSA levels after 3–6 months of initiating testosterone replacement therapy should be investigated. Our recommendations for requesting a urological consultation are provided in Table 5.

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Table 5. *Indications for urological consultation in men receiving testosterone replacement*

Men being considered for testosterone replacement therapy should also be evaluated for prostate symptom scores by using the AUA or the IPSS symptom questionnaires. Testosterone should not be administered to men with symptoms scores in excess of 21. These symptom scores should be re-evaluated 3 months after initiating testosterone replacement therapy, and annually thereafter. Marked increases in PSA symptom scores or increases above 21 during treatment should lead to urological evaluation.

Other Uncertainties Related to Testosterone Supplementation in Older Men

Although this review focused on issues related to potential prostate adverse events and monitoring during testosterone replacement of older men, a number of other uncertainties are related to the issue of testosterone supplementation, which have been discussed in other recent reviews (Andropause Consensus Panel 2001; AACE Guidelines for Evaluation and Treatment of Hypogonadism in Adult Male Patients 2002 Update; Bhasin and Buckwalter 2001; Matsumoto 2002; American College of Medicine, 2002; Morales and Lunenfeld 2002), but were not covered in this systematic review. There is no consensus on numerical thresholds of serum total or free testosterone concentrations, which should be used to define "androgen deficiency" in older men. However, most authorities compare levels with those in healthy men 20 to 40 or 45 years of age. The beneficial effects of testosterone replacement in older men on health-related outcomes are yet to be demonstrated. We do not know the optimum target level of serum testosterone that should be achieved during testosterone replacement and that would maximize benefits and minimize the risks of testosterone supplementation. The role of androgen supplements—DHEA and androstenedione—which are widely available in health food stores, remains largely unknown.

Acknowledgments and Disclaimers

These recommendations for prostate monitoring of men receiving or being considered for testosterone replacement therapy are not based on definitive data from large, long-term randomized, placebo-controlled trials; rather, they reflect the opinions of the authors that were shaped by the available data from studies of testosterone administration in young and older men of up to 3 years duration, deliberations of the Andropause Consensus Panel (2001), and the ACP-ASIM Disease Management Module on Male Hypogonadism (2002). These recommendations should be viewed as an approximate guide and are not intended to substitute for good clinical judgment and physician discretion.

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