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H. M. Behre

EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY ON PROSTATE AND BONE

Summary

As an androgen-dependent organ the prostate is an important site of effects, but also of potential side-effects of testosterone treatment. In hypogonadal patients, cross-sectional and longitudinal studies demonstrate that testosterone replacement increases prostate volume to levels of age-matched normal men without any further age-independent increase during long-term therapy. Testosterone therapy is contraindicated in men with active prostate cancer. On the other hand, no data are available so far indicating that testosterone replacement induces prostate carcinoma. However, data are very limited and close monitoring of men receiving testosterone is recommended, including regular digital rectal examination, transrectal ultrasonography and serum PSA measurements. The well-documented increase of bone mineral density (BMD) in hypogonadal men is one of the leading indications for testosterone substitution. Long-term, effective androgen therapy significantly increases both trabecular and cortical BMD in hypogonadal men independently of age and type of hypogonadism.

Zusammenfassung

Als Androgen-abhängiges Organ ist die Prostata ein wichtiger Angriffspunkt für die Wirkungen, aber auch für eventuelle Nebenwirkungen einer Testosteron-Therapie. Bei hypogonadalen Patienten zeigen Querschnitts- und Longitudinalstudien, daß eine Testosteron-Substitutionstherapie zu einer Vergrößerung der Prostata bis zu Normalwerten altersentsprechender Männer führt, ohne weitere altersunabhängige Vergrößerung in einer Langzeittherapie. Bei Männern mit Prostatakarzinom ist eine Testosteron-Therapie kontraindiziert. Andererseits gibt es keine Daten, die beweisen, daß eine Testosteron-Substitution ein Prostatakarzinom induziert. Aufgrund der wenigen verfügbaren Daten wird eine strenge Überwachung der mit Testosteron behandelten Männer empfohlen, einschließlich einer regelmäßigen digitalen Rektaluntersuchung, einer transrektalen Ultraschalluntersuchung und einer Überwachung des PSA im Serum. Die gut dokumentierte erhöhte Knochendichte bei therapierten hypogonadalen Männern ist eine der Hauptindikationen für eine Testosteron-Substitution. Eine wirksame Androgen-Langzeittherapie steigert sowohl die trabekuläre als auch die kortikale Knochendichte bei hypogonadalen Männern, unabhängig vom Alter und Art des Hypogonadismus.

Résumé

C'est dans la prostate, en tant qu'organe androgénodépendant, que s'opèrent les effets d'un traitement substitutif à la testostérone, mais elle peut également être le site d'éventuels effets non souhaités. Chez les patients avec hypogonadisme, des études transversales et longitudinales prouvent qu'un traitement substitutif à la testostérone fait augmenter le volume de la prostate jusqu'aux niveaux compatibles avec l'âge, sans aucune autre augmentation non liée à l'âge durant un traitement à long terme. Le traitement à la testostérone est contre-indiqué chez les hommes atteints d'un cancer actif de la prostate. Cependant il n'y a pas de données indiquant qu'un traitement de substitution à la testostérone provoquerait un cancer de la prostate. Quoiqu'il en soit, les données sont assez restreintes et une surveillance étroite des hommes sous traitement à la testostérone est conseillé, y compris un examen digital régulier du rectum, une échographie transrectale et une évaluation du PSA sérique. La croissance de la densité minérale osseuse chez les hommes avec hypogonadisme est bien documentée et constitue une des principales indications de traitement substitutif à la testostérone. A long terme, une thérapie efficace à l'androgène augmente vraiment à la fois le BMD trabéculaire et cortical chez les hommes avec hypogonadisme, indépendamment de l'âge et du type de l'hypogonadisme.

INTRODUCTION

The potential use of testosterone preparations for substitution therapy of hypogonadal aging men, in addition to the well-established substitution therapy of male hypogonadism, make the increased use of testosterone likely. Therefore, the risks and benefits of testosterone application prompt growing attention by physicians and scientists [1]. As the prostate is an androgen-dependent organ and prostate diseases have a high prevalence among males [2, 3], special attention should be given to potential side-effects of testosterone administration on this organ. On the other hand increase of bone mineral density in hypogonadal men seems to be one leading indication for testosterone substitution.

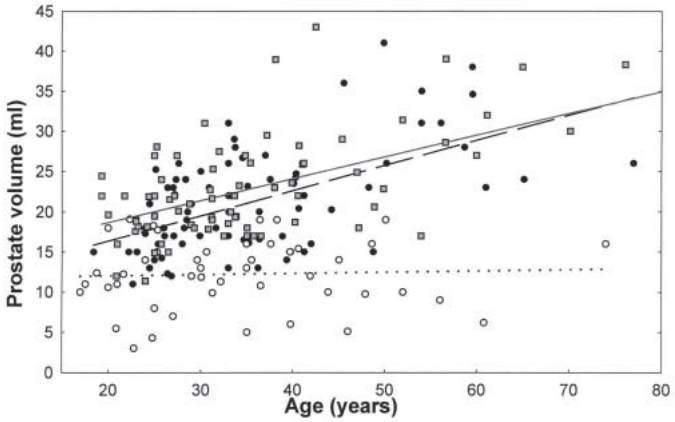
Testosterone effects on prostate function in hypogonadal and normal men

Previously we have shown in a cross-sectional study involving normal men (n = 75), newly diagnosed hypogonadal men before testosterone treatment (n = 47), and hypogonadal men with long-term effective testosterone therapy (n = 78) that prostate volume was significantly reduced in untreated hypogonadal men, while long-term effective testosterone treatment increased prostate size only to levels comparable to age-matched normal controls (Figure 1) [4]. Prostate-specific antigen (PSA) was significantly decreased in untreated hypogonadal patients, whereas testosterone-treated hypogonadal men and normal men had comparable values within the normal range. No difference in uroflow parameters was detected between the three groups. We also compared prostate function between hypogonadal patients treated with the standard therapy of intramuscular testosterone enanthate and transscrotal testosterone replacement. Serum levels of dihydrotestosterone were significantly higher in transscrotal testosterone-treated compared to testosterone enanthate-treated patients, whereas serum testosterone, estradiol, and sex-hormone binding globulin were comparable. Independent of dihydrotestosterone serum levels, prostate volume and PSA levels were in the age-related normal range and not significantly different between both treatment groups [4].

In a prospective longitudinal study of androgen replacement with non-scrotal testosterone patches, prostate volume increased significantly in 29 hypogonadal men after 3 months of testosterone replacement and remained unchanged for the next nine months up to the end of the study [5]. We were interested whether there might be a steady increase of prostate volume during several years of continuous testosterone substitution. In a 10-year study involving 11 hypogonadal men treated with scrotal testosterone patches, prostate volume increased insignificantly in the nine patients aged less than 50 years from 16.8 ± 1.5 to 18.8 ± 2.1 ml during testosterone replacement, whereas PSA levels remained unchanged. In the two older patients, prostate volume remained unchanged during the observation period [6]. These small-scale longitudinal studies provide evidence that long-term therapy with androgen preparations leading to testosterone levels in the normal range might not induce benign prostatic hyperplasia.

In normal men, treatment with high doses of 200 mg testosterone enanthate every week for 12 months resulted in a small but significant increase (14 ± 2 %) of prostate volume in four of five volunteers [7]. No change was seen in serum levels of PSA. So far, experience with high-dose testosterone on the prostate in normal men is limited, and further prospective, assessor-blinded studies with different doses of testosterone applying transrectal ultrasonography and PSA measurements are clearly needed.

Figure 1: Scattergram and regression lines of prostate volume measured by transrectal ultrasonography versus age in hypogonadal men before testosterone therapy (○, *dotted line*), long-term testosterone-treated hypogonadal men (□, *medium dashed line*) and normal men (●, *solid line*) (adapted from [4]).



Testosterone and prostate cancer

Testosterone therapy is contraindicated in patients with existing prostate cancer. The regression of prostate cancer after androgen deprivation is well recognized and indicates that the majority of

prostate cancer cells are partially androgen-dependent, at least initially.

However, the role of androgens in the initiation of prostatic cancer is not exactly understood [2, 3, 8]. A series of genetic and phenotypic alterations are involved in the multistep nature of prostate carcinogenesis [2]. There are numerous inconsistent reports from the literature indicating that testosterone levels in prostate cancer patients can be elevated, unchanged or reduced [3]. Epidemiological investigations have failed to demonstrate consistently that circulating levels of sex hormones and their binding proteins are implicated in the etiology of prostate cancer. In contrast, recent epidemiological studies unequivocally link serum insulin-like growth factor 1 (IGF-1) levels to a risk for prostate carcinoma [9].

It could be concluded that sex steroids do not play a major role in the etiology of prostate cancer. Perhaps the effects of sex steroids are mediated by differences in androgen receptor expression or function, or intracellular androgen levels. However, it should be noted that the negative results of some epidemiological studies could be due to their relatively small size or lack of adjustment for confounding factors.

Recently, the first meta-analysis on testosterone as a predictor of risk of prostate cancer development was published [10]. This analysis was restricted to studies that performed mutual adjustment for all measured serum hormones, age, and body mass index. It was concluded that men whose total serum testosterone is in the highest quartile are 2.34 times more likely to develop prostate cancer than those in the lowest quartile (95 % confidence interval, 1.30 to 4.20). Neither DHT nor estradiol levels were significantly associated with the development of prostate cancer. Men with highest SHBG levels were less likely to develop prostate cancer relative to those with the lowest levels (adjusted odds ratio, 0.46; 95 % confidence interval, 0.24 to 0.89). This suggests that circulating bioavailable testosterone could be more important in the development of prostate cancer than total testosterone. All studies included in the meta-analysis which examined the role of serum IGF-1 consistently demonstrated a positive and significant association with prostate cancer risk which is similar in magnitude to that of testosterone. One recent longitudinal case-control study in Finland, which was not included in the first meta-analysis, just failed ($p = 0.06$) to detect a significant association between serum testosterone and the occurrence of subsequent prostate carcinoma [11].

These epidemiological studies do not provide evidence for the suspicion that testosterone administration to normal men for male contraception or to hypogonadal aging men will induce prostate carcinoma. To date, no real long-term follow-up studies addressing this issue in testosterone-treated men have been performed. Therefore, based on the information available up to now the following recommendations can be given:

- For male contraception or treatment of hypogonadal men only those testosterone preparations should be applied which avoid serum levels of testosterone in the high normal or supraphysiological range.
- Men treated with testosterone should be monitored carefully by trained physicians for side-effects on the prostate. It should be noted that a significant number of older men with low testosterone levels have biopsy-detectable prostate cancer despite normal PSA levels and normal digital rectal examination [12]. It has been suggested that patients with histological prostate cancer and initially normal PSA levels will respond with a significantly higher increase of PSA [13] than healthy men [4]. For this reason, we recommend close monitoring of PSA levels at the initiation of testosterone therapy, followed by regular controls including rectal palpation, transrectal ultrasonography, and PSA measurements every 3–6 months during long-term testosterone therapy in the aging male.

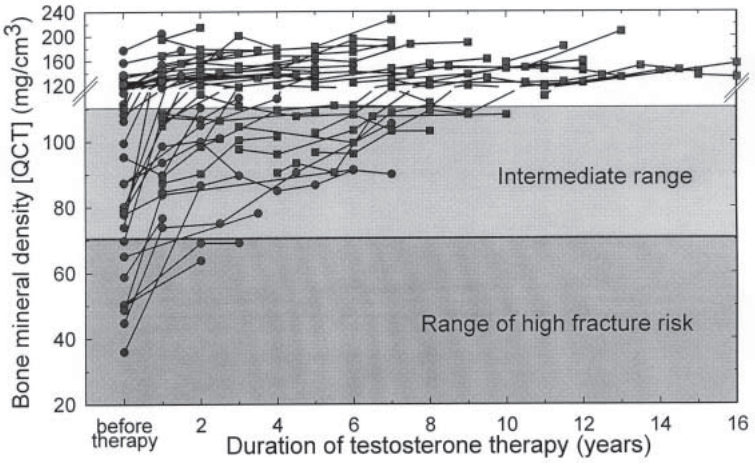
Testosterone effects on bone

One of the prominent clinical symptoms of testosterone deficiency in men is a significant decrease in bone mineral density (BMD) [14]. Case-controlled studies have demonstrated that in hypogonadal men this reduced BMD is associated with a significant increase in bone fractures [15]. The biological action of testosterone on bone is of high clinical and socioeconomic relevance, as the prevalence of hypogonadism increases signifi-

cantly in elderly men and exceeds 20 % in men over 60. Along with lower testosterone levels a clear decrease in BMD and an increase in hip and spine fractures [16] have been demonstrated in aging males, similar to the well-described changes in postmenopausal women. Large multicenter clinical trials have shown that estrogen replacement therapy prevents loss of BMD and decreases the incidence of bone fractures, which in untreated women are caused by the decrease in endogenous estrogens after menopause.

Only recent studies could demonstrate a beneficial effect of long-term testosterone substitution therapy on bone in men. We investigated BMD changes in hypogonadal men treated with testosterone preparations for up to 16 years [17] (Figure 2). In this study we demonstrated that decreased BMD due to hypogonadism can be restored to the age-dependent reference range by effective, long-term androgen substitution therapy. The largest increase was seen in patients with initial low BMD during the first year of treatment. Our results are similar to those obtained in postmenopausal women receiving estrogen replacement therapy, where therapy is most effective during the first year of treatment, and the magnitude of the BMD increase is greatest in those women with low initial BMD. In our study we did not assess the incidence of fractures in hypogonadal patients. However, testosterone deficiency is an important risk factor for fractures in men, and in women it has been clearly demonstrated that long-term, continuous estrogen hormone replacement therapy that increases BMD reduces the individual risk of bone fractures [18].

Figure 2: Increase in BMD during long-term testosterone substitution therapy up to 16 years in 72 hypogonadal patients. Circles indicate hypogonadal patients with first QCT measurement before initiation of testosterone substitution therapy, squares show those patients already receiving testosterone therapy at the first QCT. The dark shaded area indicates the range of high fracture risk, the unshaded area shows the range without significant fracture risk, and the light shaded area indicates the intermediate range where fractures may occur (adapted from [17]).



In contrast to previous studies we demonstrated that effective androgen therapy increases BMD in hypogonadal patients independent of age. The oldest patient in our series was 74 years old when he was first, remarkably late, diagnosed to have Klinefelter syndrome. His trabecular BMD increased by intramuscular testosterone injections from 36 to 87 mg/cm^3 within 2 years. Another patient with idiopathic hypogonadotropic hypogonadism was first diagnosed at the age of 61 years. During treatment with intramuscular testosterone enanthate, his trabecular BMD increased from 49 to 85 mg/cm^3 within 12 months. Statistical analysis in all 72 patients of our study revealed that testosterone therapy is an age-independent, highly significant factor influencing BMD. Hypogonadal patients with reduced BMD will benefit from long-term, effective androgen substitution therapy, and thus, age per se should not preclude patients from appropriate treatment.

In an follow-up study we investigated the long-term effect of testosterone replacement therapy on spinal bone and muscles. The trabecular and cortical BMD, vertebral body area and paraspinal muscle area were assessed by QCT in 32 testosterone-substituted patients, aged 18–74 years, with idiopathic hypogonadotropic hypogonadism, pituitary insufficiency, Klinefelter syndrome or other forms of primary hypogonadism [19]. They were followed for a mean period of 3.2 ± 1.7 years (mean ± SD), ranging from 1 to 7 years. A significant increase in trabecular and cortical BMD was documented in the course of

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Born 1961 in Paderborn, Germany. 1980–1987 Medical studies at the Westphalian Wilhelms-University (WWU) in Münster, the University of London, the University of Washington in Seattle and the Harvard Medical School in Boston. M.D. Degree. 1987–1988 Research fellow of the Max-Planck-Society in the Clinical Research Group on Reproductive Medicine in Münster. Dr. med. Degree. 1988–1990 Clinician and Scientist at the Institute of Reproductive Medicine of the WWU in Münster. 1990–1997 Senior Physician at the Institute of Reproductive Medicine. Since 1994 member of the Human Reproduction Program of the World Health Organization (WHO). 1994 Clinical Andrologist (European Academy of Andrology). 1995 Habilitation and Assistant Professor in Andrology and Reproductive Medicine. 1997–2000 Associate Professor and Head of the IVF-Unit of the Center for Gynecology of the WWU in Münster. 1999 Board Certificate in Obstetrics and Gynecology, Gynecological Endocrinology and Reproductive Medicine. Since 7/2000 Full Professor in Andrology at the Department of Urology of the Martin-Luther-University in Halle, Germany.

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replacement therapy in all patients regardless of the type of hypogonadism and age of patients. A slight but significant increase in paraspinal muscle area was observed if all patients were taken together. The area of paraspinal muscle correlated with body weight and moderately with trabecular BMD. The effects seen on paraspinal muscles emphasize the clinical benefit of adequate replacement therapy for the physical fitness of hypogonadal men. Vertebral body area did not change over time. It correlated only with height and weight but not with BMD.

In summary, our studies demonstrate that long-term, effective androgen therapy significantly increases both trabecular and cortical BMD in hypogonadal men independently of age and type of hypogonadism.

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