Testosterone Supplementation in Hypogonadal Men on 5-ARI Therapy

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ABSTRACT

Introduction. Hypogonadism and benign prostatic hyperplasia (BPH) often coexist in the aging man. Treatment of these conditions would seem to be inconsistent as BPH is treated often with 5-alpha reductase inhibitors (5-ARIs) that have impact on the active form of testosterone dihydrotestosterone (DHT), while the treatment of hypogonadism is aimed at raising testosterone to alleviate the symptoms of hypogonadism. Few studies, however, have addressed the combined use of these 5-ARI medications with exogenous testosterone supplementation.
Aim. This review will examine available literature for testosterone supplementation in men taking 5-ARIs.
Methods. This review examines the data available to study this combination.
Results. Current data appear to support the safety and efficacy of combined treatment.
Conclusions. The combination for testosterone and 5-ARIs appears to be safe and efficacious, but the paucity of large long-term studies are needed to further clarify the concomitant use of testosterone and 5-ARIs in the aging male.
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Key Words. Benign Prostatic Hyperplasia; Testosterone; Finasteride; Dutasteride; Hypogonadism

Introduction

Hypogonadism is associated with loss of energy, decreased muscle bone mass, and sexual dysfunction [1]. Benign prostatic hyperplasia (BPH) causes lower urinary tract symptoms, possible urinary retention, and for some, an eventual need for BPH-related surgery [2]. BPH and hypogonadism are common in the aging male. Many symptoms of hypogonadism respond to testosterone replacement. The effect of testosterone treatment in symptomatic BPH is unknown and, for some, considered a relative contraindication. as testosterone treatment conceivably might increase prostate size and exacerbate lower urinary tract symptoms (LUTS) [1].

In the population-based Baltimore Longitudinal Study on Aging, serum testosterone levels less than 325 ng/dL were observed in approximately 20% of men over the age of 60 years, 30% over 70 years, and 50% over the age of 80 years [2]. In an analysis of patients enrolled in a BPH clinical trial, a low-serum testosterone was noted in 27%, largely concordant with the general population results [3]. In the BPH population, the prevalence of men with a serum testosterone less than 150 ng/dL was 1%, similar to that observed in the Massachusetts Male Aging Study [4]. A recent subanalysis of the baseline characteristics of men enrolled in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, a 4-year, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of dutasteride (D) for reducing the risk of biopsy-detectable prostate cancer, showed similar findings. In this group of 8,231 men in which 50% had LUTS and 80% prostate enlargement, baseline serum testosterone level was less than 300 ng/dL in 21% of subjects, 250 ng/dL in 11%, and 200 ng/dL in 4% [5].

Medical therapies indicated for men with BPH symptoms, particularly those with enlarged prostate glands (American Urological Association

[AUA] guideline reference), include the 5-alpha reductase inhibitors (5-ARIs) [6]. This class of drugs blocks the conversion of testosterone (T) to dihydrotestosterone (DHT), the hormone most responsible for the development of BPH. Finasteride (F) is a selective Type II 5-ARI that reduces serum and prostate tissue DHT levels to 65–70% and 85–90%, respectively [3]. D is a dual Type I and II 5-ARI that results in a reduction of serum and prostate tissue levels of DHT to even lower levels (85–90% and 95%, respectively) [7]. Because hypogonadal men with BPH will be potentially treated with both a 5-ARI and T supplementation, it is important to understand whether exogenous T affects the clinical response of the 5-ARI therapy. An assessment of the literature examining 5-ARI effects in hypogonadal men receiving concurrent supplemental T suggests it does.

Methods

Two studies are available in the literature examining the biochemical, hormonal, and clinical effects of 5-ARI therapy in hypogonadal men receiving exogenous T therapy.

Study 1 (Amory et al. 2004) [8]: In a study designed to determine whether a combination of T and F, might increase bone mineral density (BMD) in older men without adverse effects on the prostate, 70 men aged 65 years or older, with a serum T less than 12.1 nmol/L on two occasions, were randomly assigned to receive one of three regimens for 36 months: T enanthate, 200 mg every 2 weeks with placebo pills daily (T only); T enanthate, 200 mg every 2 weeks with 5 mg F daily (T + F); or placebo injections and pills (placebo). Total T, bioavailable T (BT), DHT, prostate-specific antigen (PSA) and prostate size (PV) were measured at baseline and during treatment to assess the impact of therapy on the prostate (Table 1).

Study 2 (Page 2005) [9]: In a study designed to determine whether combining D with T treatment in older hypogonadal men with BPH reduces androgenic stimulation of the prostate compared to T alone, 46 men with symptomatic BPH, prostate volume (PV) of 30 cc or greater and serum total T less than 280 ng/dL (less than 9.7 nmol/L) were randomized to daily transdermal 1% T gel plus oral placebo or D for 6 months. Total T, free T (FT), DHT, PSA and PV were measured at baseline and during treatment (Table 1).

Results

Study 1 [8]: Over 36 months, PSA increased significantly from baseline in the T-only group (40%; $P < 0.001$) but also increased in the T + F group as well (10%). PV increased in all groups during the 36-month treatment period, but this increase was significantly less in the T + F group (15%) compared with both the T-only and placebo groups ($P = 0.02$). The mean serum DHT levels decreased by 50% at 4 months in the T + P group (Table 2).

Study 2 [9]: Serum total T increased similarly into the mid-normal range in both groups. Serum DHT increased in the T only but decreased in the T + D group (57%). In the T + D group, PV and mean PSA decreased 12% and 35%, respectively, compared with the T-only group in which PV and PSA increased 7.5% and 19% ($P = 0.03$ and $P = 0.008$), respectively, after 6 months of treatment.

Discussion

BPH is an androgen-dependent condition. T and in particular its androgen metabolite, DHT, are required for normal prostate development, having, in general, a smaller prostate gland that eugonadal men [10]. Hypogonadal men T replacement in hypogonadal men mildly increases PV and serum PSA. Combining androgens with a 5-ARI therapy has been proposed as a prostate sparing androgen replacement regimen [11]. This would be most

Table 1 Baseline characteristics for all subjects in the two studies

Study	Intervention	N	Age (Mean years)	Total T ng/dL (mmol/L)	DHT ng/dL (mmol/L)	PSA ng/mL	PV (cc)
1 (ref 8)	Placebo	24	71	302 (10.5)	29 (1.0)	1.4	32
	T	24	71	286 (9.9)	23 (0.8)	0.9	29
	T + F	22	71	291 (10.1)	26 (0.9)	1.0	33
2 (ref 9)	T	27	64	206 (7.1)	47 (1.6)	2.9	54
	T + D	26	64	213 (7.4)	28 (1.0)	2.1	44

DHT = dihydrotestosterone; PSA = prostate-specific antigen; PV = prostate volume; T = testosterone