SEXUAL MEDICINE REVIEWS REVIEWS

Do 5α-Reductase Inhibitors Raise Circulating Serum Testosterone Levels? A Comprehensive Review and Meta-Analysis to Explaining Paradoxical Results

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ABSTRACT

Introduction: Many studies have reported that 5α-reductase inhibitors (finasteride and dutasteride) raise serum testosterone (T) levels, yet there is lack of consistency among studies on this point.

Aim: To review and meta-analyze available studies reporting changes in serum T concentrations in men treated with 5α-reductase inhibitors (5α-RIs).

Methods: A Medline search using PubMed and EMBASE was performed including the following key words: "finasteride," "dutasteride," "testosterone and 5α-reductases."

Main Outcome Measure: Relevant studies were extracted, evaluated, and analyzed. Of these, 40 studies were analyzed qualitatively and 11 were included in the meta-analysis. A random effects model was used to conduct the meta-analysis.

Results: In 11 studies comprising 1,784 patients with age ranging between 18 and 83 years and average treatment follow-up of 17 months, meta-analytic estimate of the mean baseline change was 27 (95% confidence interval 1−54). The meta-analysis did not demonstrate unequivocal significant increase in serum T levels. The increase was not uniform among all studies reported. Sensitivity analysis showed that no single study contributed decisively to the outcome or could be attributed to drug action. The reported increases in T levels with finasteride or dutasteride in men with low baseline serum T may be attributed, in part, to increased trapping of T by unsaturated sex hormone binding globulin (SHBG) due to dissociation of 5α-dihydrotestosterone. In men with high baseline T levels, there appears to be no change in serum T levels. 10 studies reported luteinizing hormone, follicle-stimulating hormone, SHBG, and estradiol values and none reported significant changes in their levels, suggesting that observed changes in serum T levels are unlikely mediated by gonadotropins levels or peripheral conversion of T to estradiol.

Conclusion: 5α-RI therapy is not associated with consistent and significant increases in serum T levels. **Traish AM, Krakowsky Y, Doros G, et al. Do 5α-reductase inhibitors raise circulating serum testosterone levels? A comprehensive review and meta-analysis to explaining paradoxical results. Sex Med Rev 2018;XX:XXX−XXX.**

Key Words: Finasteride; Dutasteride; Testosterone; 5α-Dihydrotestosterone; Luteinizing Hormone; Follicle-Stimulating Hormone

INTRODUCTION

In 1992, finasteride, a selective inhibitor of 5α-reductase type 2, was introduced as therapeutic modality for the treatment of lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH).[1] In 2002, dutasteride, a selective inhibitor of 5α-reductase types 1 and 2, was introduced for LUTS treatment in men with BPH.[2] Finasteride has also been approved for the treatment of male pattern hair loss (MPHL), also known as androgenetic alopecia (AGA).[3] Finasteride reduces progression of baldness and stimulates new hair growth.[4]

Among the most inconsistent observations reported in studies with 5α-reductase inhibitor (5α-RI) therapy are the unexplained

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discrepancies in circulating serum T levels in response to finasteride or dutasteride therapy. To date, we are unaware of any published data to resolve whether, and under what conditions, serum T levels may increase in response to 5α-RI administration, nor are there any proposed mechanisms to explain why this should occur. As shown in Table 1, a number of studies reported that finasteride and dutasteride treatments increased circulating serum T levels by 10% to 30% in men (Table 1). A similar number of studies reported either no increase or even a reduction in serum T levels with finasteride or dutasteride therapy (Table 2). Although it is widely believed that finasteride and dutasteride therapy increase serum T levels, the contemporary literature is mixed on this important issue.

Because serum T concentrations are clinically used for diagnosis of men with testosterone deficiency (TD; also known as hypogonadism), the discrepancies in serum T levels among various studies raise a fundamental clinical concern regarding the clinical implications of T increases with such agents, which has yet to be addressed in the medical literature. In addition, because T therapy is thought to ameliorate signs and symptoms of TD, one would expect that increased serum T levels in men treated with finasteride or dutasteride would have improved signs and symptoms of TD. In fact, a recent study[5] has suggested that the increased serum T levels in men treated with dutasteride may provide potential benefits in men with low baseline serum T levels and moderate late-onset hypogonadism. An editorial comment by Shigehara and Mizokami[6] on the aforementioned study suggested that the increase in serum T levels in men with low baseline serum T levels resulted in beneficial effects, such as increased bone mineral density (BMD) and reduced body mass index (BMI).[7,8]

In the study by Hong et al,[8] BMI for the entire dutasteride group (n = 33) was 25.4 ±1.9 kg/m^2 at baseline and 25.2 ± 2.2 kg/m^2 at 1 year, a mean decrease of merely 0.17 kg/m^2 ($P = .253$). When BMI data were stratified by baseline T levels, a slight change in the group (n = 14) with the lowest baseline T (<3.6 ng/dL) was noted but not in the groups (n = 9) with intermediate (3.6−5.0 ng/dL) or higher (n = 10) T levels (>5 ng/dL). The small number of patients in each group does not permit drawing general conclusions regarding the changes in BMI from this study.[8] In the second of these cited studies,[7] changes in BMI after 12 months of dutasteride were not statistically significant even in men with lower T concentrations. Regarding BMD, the ratio to reference values derived from young adult men were 105.4 ± 22.1 at baseline and 106.5 ± 22.0 at 12 months. This difference was reported as statistically significant, but the magnitude of this effect is clearly minor and unlikely to be clinically meaningful. Interestingly, in a group with a higher baseline T, no significant changes were noted for either BMI or BMD. In addition, there were no changes in muscle volume.

Importantly, there are no credible reports to date demonstrating that treatment with finasteride or dutasteride improves symptoms of TD. However, men treated with finasteride or dutasteride often develop symptoms suggestive of TD, such as loss of libido and increased incidence of erectile and orgasmic dysfunctions.[9–16] A key remaining issue is that no physiological mechanisms have been advanced to explain how 5α-RIs may increase serum T levels. In this article, we present our review of the literature regarding the impact of 5α-RIs on serum T concentrations; we performed a meta-analysis to determine if there are significant changes in serum T. As described in detail, we found no consistent rise in serum T with 5α-RIs. We propose a hypothesis for a physiological mechanism to explain observed discrepancies in serum T concentrations in the literature.

METHODS

Systematic Literature Search

Methods for the literature search, data extraction, and analysis were specified as outlined below. We performed a comprehensive literature review using the U.S. National Center for Biotechnology Information's PubMed database, an electronic search of MEDLINE (using the PubMed interface) databases, and Embase to search for relevant studies. The search, which accrued data from January 1, 1989 to November 1, 2017, included clinical trials and observational studies. This literature search for meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (http://www.prisma-statement.org).

As shown in Figure 1, our search was developed using the term ("finasteride"[MeSHTerms] OR "finasteride"[All Fields]) OR ("dutasteride" [MeSH Terms] OR "dutasteride" [All Fields]) AND ("testosterone" [MeSH Terms]. Searches using "finasteride AND testosterone" produced 718 publications (Figure 1). Searches using "dutasteride AND testosterone" produced 191 publications. Searches using "5α-reductase inhibitors (5α-RIs) AND testosterone" produced 1,014 publications, for a total of 1,923 articles. After removing duplicate publications there were 836 articles to be reviewed. A large number of articles were retrieved that did not pertain to testosterone and were eliminated. This process resulted in reduction from 836 to 450 articles. We reviewed 450 articles, which had the terms either finasteride or dutasteride and testosterone. Of these, 50 articles provided adequate data in the form of baseline and follow-up T concentrations and met general eligibility criteria for qualitative and quantitative analysis. The net number of articles that contained valuable information quantitatively or qualitatively was 40 articles. For quantitative analysis (meta-analysis), we excluded studies in which the treatment duration was <3 months and those with finasteride treatment with a dose <1 mg or >5 mg, as well as those in which dutasteride treatment with a dose <0.5 mg or >0.5 mg. We also excluded studies with drugs other than finasteride or dutasteride. This permitted evaluation of only 11 studies in the meta-analysis. These 11 studies met our inclusion and exclusion criteria, as described below. In the qualitative analysis, we included all studies reporting quantitative or qualitative serum T concentrations in response to treatment with finasteride or dutasteride in men with BPH or AGA, or

Table 1. Studies demonstrating increased T levels in response to finasteride or dutasteride therapy

Study	Subjects, n	Age range, y	Drug	Dose	Treatment duration	Study authors' comments on the effects on total T level
Gormley et al, 1992[1]	895	40–83	Finasteride	1 and 5 mg	12 mo	Serum T concentrations increased approximately 8%–10% after 2 weeks of treatment, and they remained increased thereafter. Despite the increases, all values were within the normal range at all times.
Castro-Magna et al, 1996[17]	22	16–30	Finasteride	10 mg	2 y	T concentrations were significantly increased after 3 months of finasteride treatment ($P < .005$). The effects of finasteride on hormonal levels were seen after the first 3 months of treatment, and they were maintained without significant change throughout the 2 years.
Uygur et al, 1998[20]	48	49–81	Finasteride	5 mg	6 wk followed by 3–6 mo	After 3 months of finasteride use, a 15% increase was noted in T levels ($P < .05$), and this increase reached 26% at month 6 ($P < .01$). However, all patients still had T values within the normal range both at month 3 and month 6.
Drake et al, 1999[22]	249	18–50	Finasteride	0.01, 0.05, 0.2, 1, or 5 mg	42 d	No significant dose–response effect was observed on the basis of serum T percentage change from baseline. Median serum T levels were variably increased among treatment groups, with significant increases from baseline in the placebo group (5.7%, $P = .014$), and 0.01-, 0.05-, and 1-mg finasteride groups (10.5%, 33.9%, 12.5%, respectively; $P < .002$), but nonsignificant increases in the 0.2- and 5-mg finasteride groups (3.5%, 3.7%).
Matsumoto et al, 2002[23]	157	50–75	Finasteride	5 mg	2–4 y	T levels were increased by 23% in the finasteride group and 2% in the placebo group, and remained well within the normal range for both groups.
Roehrborn et al, 2003[24]	301	45–78	Finasteride	5 mg	4-y trial	There was a modest but significant mean percentage increase from baseline in serum T ranging from 23%–24% during the 4-year study period. Finasteride treatment led to a larger mean percentage increase in T relative to placebo in the 2 lower baseline T tertiles compared with that for the upper T tertile.
Clark et al, 2004[27]	399	≥50	Finasteride and dutasteride	Once-daily dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg of finasteride	24 wk	Mean T levels increased but remained in the normal range for all treatment groups. Serum T concentrations did not exceed the upper limits of the normal range except in 1 individual in each of the placebo, 5-mg dutasteride, and finasteride groups.
Iranmanesh and Veldhuis, 2005[46]	9	19–34	Dutasteride	5 mg once and then 1 mg daily	3 wk	Total T increased significantly and attributed to the non-pulsatile T secretion.
Olsen et al, 2006[26]	416	21–45	Dutasteride or finasteride	Dutasteride 0.05, 0.1, 0.5 or 2.5 mg; finasteride 5 mg	24 wk	Serum T levels rose significantly in all active treatment groups, increasing by a median of 27.5% in the 2.5-mg dutasteride group compared with 10.4% in the finasteride group. In the 0.5-mg dutasteride group, the median increase at 24 weeks was 23.8%, which is similar to previous findings.

(continued)

Table 1. Continued

Study	Subjects, n	Age range, y	Drug	Dose	Treatment duration	Study authors' comments on the effects on total T level
Amory et al, 2007[50]	99	18–55	Dutasteride/ Finasteride	0.5 mg/5 mg	12 mo	T increased significantly from baseline by approximately 25%.
Hong et al, 2010[8]	120	45–75	Dutasteride	Tamsulosin 0.2 mg/ day, dutasteride 0.5 mg/day, or tamsulosin 0.2 mg plus dutasteride 0.5 mg/day	1 y	The dutasteride (n = 33) and combination groups (n = 37) had significantly greater increases in serum T level (16.3% and 15%, respectively).
Stanczyk et al, 2013[28]	53	57–79	Finasteride	5 mg	12 mo	T increased significantly from baseline (approximately 18.3%).
Shigehara et al, 2014[6]	76	>50	Dutasteride	0.5 mg	12 mo	Free T was increased in men with low baseline T but not in men with high baseline T levels.
Upreti et al, 2014[25]	46	20–85	Finasteride or dutasteride	5 mg or 0.5 mg, respectively	3 mo	T levels were increased but remained within the normal range.
Maeda et al, 2017[5]	110	NR	Dutasteride	0.5 mg	3 mo	Total T and free T increased, although mainly in men with low baseline T.

NR = not reported; T = testosterone.

screening for prostate cancer. The principal source of information was derived from published articles (Tables 1 and 2). It is important to note that although some of the studies evaluated in this review reported blood withdrawal between 8 AM and 12 noon, others did not report times of blood drawing. For this reason, it is not feasible to assess the effects of diurnal variations in T levels among these studies due to variations in timing of blood withdrawal for T measurements.

Study Protocol

Inclusion criteria for meta-analysis: Studies meeting all of the following criteria were included:

1. Published studies irrespective of date of publication
2. Manuscripts available in the English language
3. All studies pertained to human subjects who were treated for benign prostatic hyperplasia or androgenetic alopecia
4. Randomized clinical trials, as well as observational studies and reviews
5. Treatment duration ≥3 months
6. Studies with patients treated with finasteride (1- or 5-mg doses only) or dutasteride (0.5-mg dose only)

Exclusion criteria for meta-analysis: Studies were excluded if any of the following criteria were not met:

1. Serum T levels were not provided in numerical quantitative values and were only provided either as a percentage change or a general statement indicating no changes in T levels from baseline values
2. Treatment duration <3 months
3. Finasteride dose <1 mg or >5 mg
4. Dutasteride treatment with a dose <0.5 mg or >0.5 mg
5. Studies with drugs other than finasteride or dutasteride

Data Selection and End Points

The primary objective of the meta-analysis was to evaluate the effects of 5α-RI therapy (finasteride and dutasteride) on serum T concentrations. Data extracted from each study included the number of subjects, age range, drug utilized, drug dose and duration of treatment, and baseline serum T concentrations.

Statistical Analysis

The principal outcome of this analysis was the effect of 5α-RI treatment on total serum T concentrations. We used quantitative changes in serum T levels from baseline, with ≥3 months of therapy with 1 mg or 5 mg of finasteride or 0.5 mg of dutasteride, as an outcome in our analysis. We used change in T levels from baseline to a time point ≥3 months from initiation of treatment. To accommodate the anticipated heterogeneity across studies, we used random effects meta-analysis to synthesize the mean changes from baseline. In particular, we used a Bayesian hierarchical model to estimate the random effects model. Heterogeneity across studies were assessed using the Cochran Q test and I^2 statistics. Posterior

Table 2. Studies demonstrating either no changes or decrease in T levels in response to finasteride or dutasteride therapy

Study	Subjects, n	Age range, y	Drug	Dose	Treatment duration	Study authors' comments on the effects on total T level
Rittmaster et al, 1989[43]	12	50–71	MK-906 (finasteride)	10, 20, 50, and 100 mg of MK-906	24 h	Serum T levels after each dose were not significantly different from baseline ($P > .20$).
Gormley et al, 1990[21]	42 30	19–46 40–77	Finasteride	25, 50, and 100 mg or 0.04–1 mg	11 d 14 d	After 11 days of therapy, T levels were unchanged in the placebo and 25-mg treatment group but were increased in the 2 highest treatment groups (50 mg once each morning and 50 mg twice each day), which had statistically significant increases from baseline. Significant increases in T were observed only in the 1-mg group and only during the first 8 days of treatment.
Vermeulen et al, 1991[38]	NR	NR	Finasteride	1 mg	7 d	Plasma T and estradiol levels were unaffected, and luteinizing hormone levels did not change.
McConnell et al, 1992[40]	69	47–77	Finasteride	1–100 mg	7 d	Oral administration of finasteride, a 4-azasteroid inhibitor of 5α-reductase, decreased serum 5α-DHT levels but had little effect on serum T.
Rittmaster et al, 1992[51]	20	25–38	Finasteride	10–100 mg	28 d	Significant rise in baseline T from 17.6 ± 2.0 to 18.3 ± 2.3 nmol/L was seen at 14 days ($P = .046$) but not at 28 days.
Matzkin et al, 1992[37]	23	58–79	Finasteride	1 mg/day to 5 mg/day	6–12 mo	Mean serum T levels at 6 and 12 months did not change significantly from baseline in any treatment group ($P > .3$).
Dallob et al, 1994[41]	10	30–35	Finasteride	5 mg	28 d	Finasteride decreased the mean serum 5α-DHT concentration from 1.36 ± 0.18 nmol/L (n = 8) at baseline to 0.46 ± 0.10 nmol/L on day 28 and had no effect on serum T.
Van Hecken et al, 1994[65]	16	20–27	MK-0434	0.1, 1.0, 10, and 50 mg of MK-0434	0, 4, 24, and 48 h post dose	Apart from a significant increase in T vs placebo at the 1-mg dose and 5-mg dose (both at 24 hours post dose and probably a result of chance differences), there were no significant differences in T levels between the various treatments within the 2 panels at the 24- and 48-hour time points.
Schwartz et al, 1996[18]	16 10	21–25 24–47	MK-386 Finasteride	0.1–100 mg of MK-386 5 mg	19 d	No consistent effect on T concentrations was evident. Small increases in serum T were observed with finasteride alone and in combination with MK-386 (approximately 10% and 19%, respectively).
Schwartz et al, 1997[19]	20	18–45	MK-386	0.1, 0.5, 5, 20, and 50 mg	14 d	No significant alterations in serum T were observed after any dose of MK-386.
Denti et al, 2000[42]	28	55–74	Finasteride	5 mg	6 mo	After 3 and 6 months of treatment with finasteride, a significant decrease of 5α-DHT concentration was observed (52% and 56%, respectively). However, no significant changes in free T, estradiol, and SHBG concentrations were found.
Ryu et al, 2006[66]	21	23–52	Finasteride	1 mg	5 mo	No difference in the concentration of T in the plasma was observed.
Caserini et al, 2014[39]	24	18–65	Finasteride	Topical gel 0.25%	7 d	No relevant changes occurred for plasma T with either treatment.
Traish et al, 2015[15]	470	47–68	Finasteride	5 mg	36 mo	Significant decreases in serum T levels were recorded.
Traish et al, 2017[35]	230	52–72	Dutasteride	0.5 mg	36 mo	Significant decreases in serum T levels were recorded.

DHT = dihydrotestosterone; NR = not reported; T = testosterone.

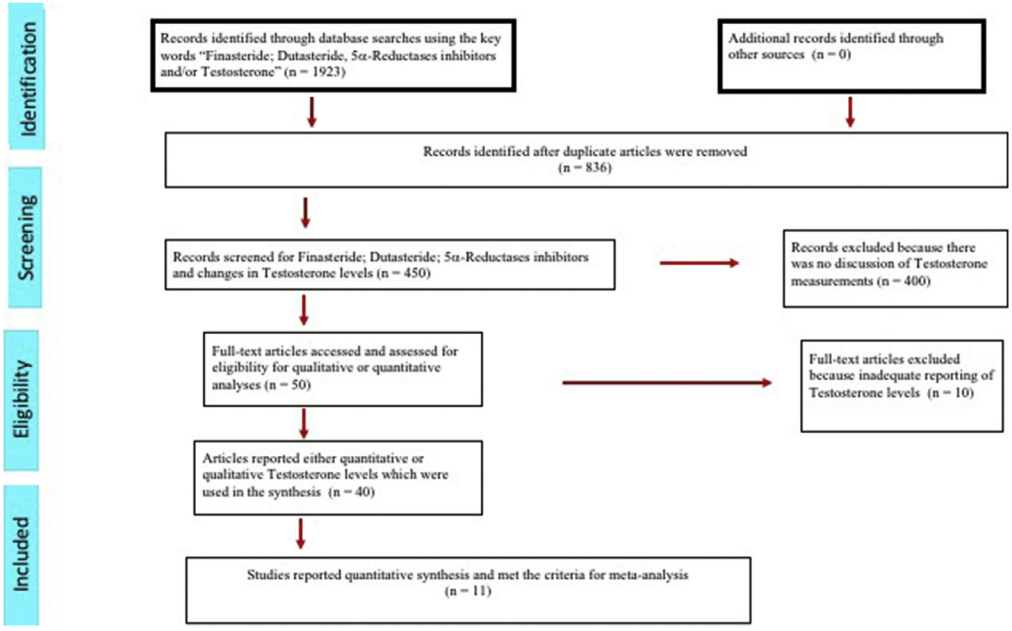


Figure 1. Flow diagram of literature search and study selection. Adopted from Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:7.

inferences (HR and 95% confidence intervals [CI]) were calculated by sampling from the posterior distribution of the parameters. Sensitivity analyses were performed to evaluate the independent effect of finasteride and dutasteride on serum T levels. Sensitivity analyses were also conducted to assess whether any of the included studies had a large influence on the results by repeating the analyses omitting 1 study at a time.

Qualitative Analyses

1. Studies Reporting Increased Serum T Concentrations With Finasteride or Dutasteride Therapy

As shown in Table 1, a number of studies reported a modest increase in serum T levels in response to finasteride or dutasteride treatment. For example, Castro-Magana et al[17] reported serum T concentrations were significantly increased after 3 months of finasteride treatment ($P < .005$) and were maintained without significant changes throughout the 2 years of therapy. Similarly, Schwartz et al[18,19] reported that small increases in serum T were observed (approximately 10% and 19%, respectively) with finasteride alone, as well as in combination with MK-386 (4,7β-dimethyl- 4-aza-5α-cholestan-3-one, an azasteroid that specifically inhibits the human 5α−R type 1 isozyme). Interestingly, however, Uygur et al[20] reported that after 6 weeks of finasteride treatment a 15% increase was noted in serum T levels ($P < .05$) measured at 3 months and this increase reached 26% measured at month 6 ($P < .01$). It should be noted that all patients had serum T values within the normal physiological range both at 3 and 6 months of therapy. One striking observation that cannot be easily reconciled in this study, was that follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels decreased by 24% and 16%, respectively. The authors reported that changes in the serum T, 5α-dihydrotestosterone (5α-DHT), FSH, and LH levels were more evident after 6 months. No significant changes were noted in the serum levels of prolactin, aldosterone, cortisol, and dehydroepiandrosterone (DHEA). The authors concluded that continued administration of finasteride (5 mg/day) altered serum levels of T, 5α-DHT, FSH, and LH significantly but provided no biochemical or endocrinological bases for such discrepancies in hormonal concentrations.

Gormley et al[21] showed a significant reduction in 5α-DHT at all doses of finasteride (1.0 mg, 0.2 mg, 0.12 mg, 0.04 mg), yet a significant increase in T and androstenedione (A-dione) were noted only with very high doses of 50 and 100 mg. The authors reported no change in LH, FSH, cortisol, or estradiol (E_2) levels. In a subsequent report, Gormley et al[1] reported that serum T concentrations increased approximately 8% to 10 % after 2 weeks of treatment with 1 or 5 mg of finasteride and remained at this higher level thereafter. All T values remained within the normal range at all time points. Drake et al[22] reported an inconsistent dose-response effect. Median serum T levels increased from baseline in the placebo group (5.7%, $P = .014$), and in the 0.01-, 0.05-, and 1-mg finasteride groups (10.5%, 33.9%, 12.5%, respectively; $P < .002$), but no significant increase was observed in the 0.2- and 5-mg finasteride groups (3.5%, 3.7%; $P > .05$). Also, serum T levels at the dose of 1 mg were not different from the placebo group. It is perplexing that a large increase in T levels was noted with the low dose of 0.05 mg of finasteride, but none was observed with a standard dose of 5 mg. The authors concluded that "no significant dose response effect was observed on the bases of serum T percent change from baseline." Clearly, there is no dose-response effect. Matsumoto et al[23] reported that T levels increased by 23% in the finasteride group and 2.0% in the placebo group. T levels remained well

within the normal physiological range for both groups. Roehrborn et al[24] showed an increase in serum T ranging from 23% to 24% during a 4-year study period with 5 mg of finasteride (Figure 2).

A critical observation made by Roehrborn et al[24] was that serum T levels increases were greatest in patients who had the lowest baseline serum T levels (<330 ng/dL) and were smaller with higher baseline serum T levels (>471 ng/dL) (Figure 2). A similar finding was reported by Hong et al[8] with dutasteride treatment for 1 year. Increases in serum T levels were greatest in men in the lowest T tertile (<360 ng/dL) and serum T actually decreased in men in the highest tertile (>500 ng/dL) (Figure 3).

A recent study by Upreti et al[25] showed small yet significant changes in T levels in response to dutasteride or finasteride. Recently, Maeda et al[5] reported increases of total T, free T, and LH after 3 months of dutasteride treatment, by 16.8%, 20.4%, and 18.5%, respectively. The authors reported that increases in serum T levels were seen primarily among patients with low baseline T levels. A negative correlation was observed between baseline serum total T levels (correlation coefficient 0.368, $P < .001$) and free T (correlation coefficient 0.378, $P < .001$) and their percentage increases after dutasteride treatment. These findings are consistent with those reported by Roehrborn et al[24] (Figure 2) and Hong et al[8] (Figure 3), although the clinical significance of these changes is uncertain (Table 1).

Olsen et al[26] reported that serum T levels rose significantly in a number of dutasteride and finasteride active treatment groups. At 24 weeks there was a median increase of 27.5% with 2.5 mg of dutasteride, 23.8% with 0.5 mg of dutasteride, and 10.4% with 5 mg of finasteride.

Clark et al[27] also investigated 399 patients with BPH who were randomized to receive once-daily dosing for 24 weeks of dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg of finasteride, or placebo. The mean percentage decrease in 5α-DHT was 98.4 ± 1.2% with 5 mg of dutasteride and 94.7 ± 3.3% with 0.5 mg of dutasteride. This value is significantly lower ($P < .001$) and with less variability than the 70.8 ± 18.3% suppression of 5α-DHT observed with 5 mg of finasteride. Mean serum T levels increased but remained within the normal range for all treatment groups.

In all these studies, the increased serum T remained within the normal physiological range. Stanczyk et al[28] reported that both T and androstenedione increased significantly from baseline. The 34.5% increase in A-dione was nearly double the increase noted in T levels (18.3%). Duskova et al[29] reported an increase in T, A-dione, and the free T index with finasteride treatment. Zhao et al[30] reported that increases in serum T levels were significantly higher with epristeride compared with finasteride (20% and 42%, respectively, $P < .001$).

The observation that increases in serum T were observed primarily in men with lower serum T concentrations provides key information for elucidating a mechanism by which 5α-RIs influence T concentrations. The increase appears unlikely to be due to de novo synthesis of T by the testes but may be attributed to either reduced metabolism and clearance rates of T or re-establishing a new equilibrium in the serum resulting in binding of T to SHBG, due to sites vacated by dissociation of 5α-DHT, upon inhibition of its synthesis.

Maeda et al[5] suggested that the increase of endogenous free T and total T in response to dutasteride therapy might bring additional improvement in aging male-related symptoms, especially in patients with lower free T baseline levels and moderate-to-poor aging-related symptoms. However, dutasteride treatment has not been shown to improve the aging male symptom (AMS) score, and inhibition of 5α-reductases is associated with decreased glucose disposal and increased insulin resistance (IR) and increased lipid accumulation in the liver[24,31–34] and worsening of AMS scores, liver function enzymes, and erectile dysfunction (ED).[14,15,35] Shigehara et al[6,17] reported that men with low baseline T had an international index of erectile function (IIEF-5) of 5.9 (± 6.6), which after dutasteride treatment did not improve or worsen and remained at 5.6 (± 6.4), $P = .107$. Men with high baseline serum T had an IIEF score of 8.1 (±7.6) but this was reduced to 5.9 (± 7.7) with dutasteride therapy.

2. Studies Reporting Either No Significant Changes or Reductions in Serum T Levels With Finasteride or Dutasteride Therapy

In contrast to the studies described in Table 1, other published reports did not demonstrate significant increases in serum T levels in response to finasteride or dutasteride therapy (Table 2). Gormley et al[21] investigated the effects of finasteride on serum 5α-DHT and T during 14 days of treatment and 14 days of discontinuation of drug. Finasteride was administered at daily doses of 1.0 mg, 0.2 mg, 0.12 mg, 0.04 mg, or placebo. The authors reported significant reductions in 5α-DHT levels with finasteride treatment and 5α-DHT levels recovered partially after drug discontinuation. However, serum T levels did not rise with these various doses of finasteride. Matzkin et al[36,37] also reported no significant changes in serum T levels after prolonged treatment with finasteride.

Vermeulen et al[38] showed that during chronic treatment with finasteride (5 mg/day), serum T and E_2 remained unaffected and LH levels did not differ significantly. Similarly, Caserini et al[39] reported no relevant changes in serum T levels with 5α-RIs therapy. McConnell et al[40] reported that increasing daily doses (1, 5, 10, 50, and 100 mg) of finasteride decreased serum 5α-DHT levels by 80% at the high doses, but no significant concomitant increases in serum T concentrations, especially at the very high doses of finasteride (Figure 4).

Dallob et al[41] reported that finasteride treatment decreased mean serum 5α-DHT concentration from 1.36 ± 0.18 nmol/L (n = 8) at baseline to 0.46 ± 0.10 nmol/L on day 28 but had no effect on serum T levels. Denti et al[42] showed that free T did not change significantly in men treated with finasteride for 3 to 6

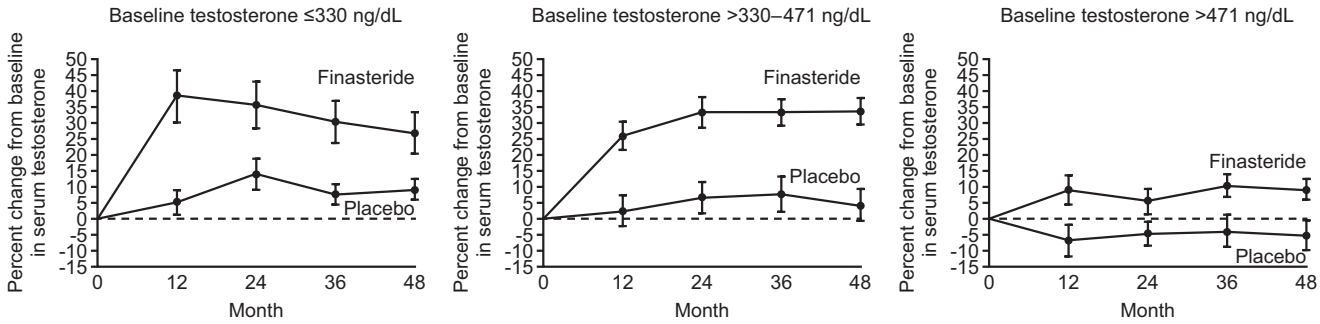


Figure 2. Mean (± SE) percentage change from baseline in serum testosterone over time, by baseline testosterone tertile. From Roehrborn CG, Lee M, Meehan A, et al. Effects of finasteride on serum testosterone and body mass index in men with benign prostatic hyperplasia. Urology. 2003;62:894–899 with permission.

months. Free T concentrations at baseline in the control and finasteride treated groups were 56.6 and 58.4 pmol/L, respectively. After 3 months of treatment, these values were 58.8 vs 61.1 pmol/L, respectively. After 6 months of therapy, these values approached 57.6 vs 56.6 pmol/L, respectively. Rittmaster et al[43] also reported no significant differences in serum T levels with increasing doses of finasteride as compared with placebo. It is clear from the data discussed above that there are considerable discrepancies in serum T levels reported in the various studies in response to treatment with finasteride or dutasteride. However, it remains unclear why such considerable and vast discrepancies exist between different studies (Tables 1 and 2).

Quantitative Analysis

Meta-Analysis of Studies Reporting Changes in Serum T Concentrations in Response to Finasteride or Dutasteride

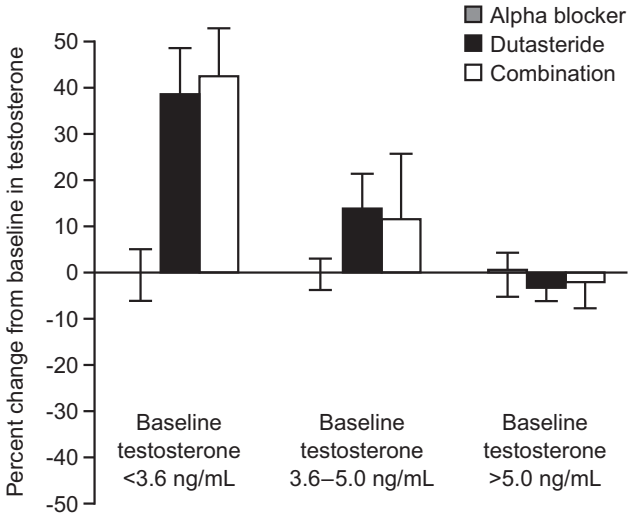


Figure 3. The mean percentage change in serum testosterone levels from baseline after 1 year of treatment in the 3 groups analyzed according to baseline serum testosterone tertile. From Hong SK, Min GE, Ha SB, et al. Effect of the dual 5alpha-reductase inhibitor, dutasteride, on serum testosterone and body mass index in men with benign prostatic hyperplasia. BJU Int 2010 Apr;105(7):970–974 with permission.

After rigorous review of the available literature, 11 studies were deemed appropriate for inclusion in a meta-analysis (Table 3). Several studies included both finasteride and dutasteride as therapeutic modalities. The studies used in the meta-analysis comprised 1,748 subjects, ranging in age between 18 and 83 years, with an average follow-up of 17 months.

Results of this meta-analysis demonstrated that serum T concentrations did not rise significantly in men treated with finasteride or dutasteride (Figure 5). Across individual studies, finasteride or dutasteride therapy were associated with very small increase in serum T levels but this increase is not consistent among all studies reported (Q 140.03, $P = .001$; $I^2 = 90\%$] with a meta-analytic estimate of the mean change in T levels of 27 (95% CI 1-54) (Figure 5). None of the studies had a large influence on the final results. This indicates a significant change, however, the estimate of the lower of the 95% CI is 1, which suggests that the change could actually be very close to 0.

7 studies reported a significant increase in serum T levels, of which 4 reported mean increases <70 ng/dL. 4 studies revealed no increase in serum T. There was considerable heterogeneity among the studies reported (Figure 6). Variation among the studies included type of study (observational vs clinical trials), drug used, dose used, duration of treatment, the medical condition of subjects treated, and the assay method used to measure total serum T concentrations. Such variabilities are reflected in the reported heterogeneity shown in Figure 6 and is accounted for in our analysis using a random effects model. Overall, serum T concentrations were not significantly increased in response to treatment, irrespective of duration or drug dose or the nature of the drug used (Figure 7).

Several questions merit vigorous discussion regarding the potential endocrine mechanisms responsible for the reported discrepancies in serum T levels associated with finasteride or dutasteride therapy. These include:

1. Are the reported increases in serum T levels associated with finasteride and dutasteride therapy due to de novo testicular T synthesis?
2. Are the reported increases in serum T levels associated with finasteride and dutasteride therapy attributed to feedback

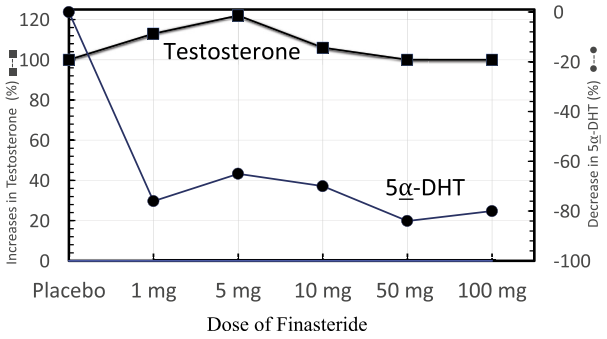


Figure 4. Percentage changes in serum T and DHT in Men treated with daily finasteride at varying doses ranging from 1 to 100 mg. Adopted from McConnell JD, Wilson JD, George FW, et al. Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Clin Endocrinol Metab 1992;74:505–508.

mechanisms due to increased synthesis and secretion of gonadotropins (LH and FSH)?

3. Can the reported increase in T levels associated with finasteride or dutasteride therapy be explained by reduced conversion of T to 5α-DHT?
4. Are the reported increases in serum T levels associated with finasteride and dutasteride therapy due to E_2 mediated increase in synthesis of SHBG?
5. Are the reported increases in serum T levels associated with finasteride and dutasteride therapy due to reduced 5α-DHT concentrations, thus vacating more binding sites on SHBG for increased T binding?

In the following section, we attempt to answer these questions based on available data and propose a mechanism that explains the discrepancies in changes in serum T among various studies.

1. Are increases in serum T levels associated with finasteride or dutasteride therapy attributed to de novo testicular T synthesis?

A comprehensive survey of the literature produced few reports suggesting that inhibition of 5α-RI increases testicular T biosynthesis. Castro-Magana et al[17] proposed that finasteride increased the activity of the 17-ketosteroid reductase enzyme resulting in the improvement in testicular capacity for T production induced by finasteride. However, no experimental evidence was provided. Studies by Fruzzetti et al[44] and Rittmaster et al[45] showed that finasteride had no influence on adrenal steroidogenesis. Iranmanesh and Veldhuis[46] postulated that inhibition of 5α-R types 1 and 2 preferentially drives nonpulsatile T secretion in healthy men. They postulated that intratesticular 5α-reduced androgens repress basal Leydig cell steroidogenesis and therefore, inhibition of 5α-reduced metabolites would enhance T secretion.

Rittmaster et al[47] suggested that the decrease in 5α-DHT levels with dutasteride was accompanied by a reciprocal increase in serum and intraprostatic T levels. However, the intraprostatic T levels in the dutasteride-treated group generally remained lower than the intraprostatic 5α-DHT levels in the control group. Significant increases in serum T levels of about 25% were observed in both the dutasteride and finasteride treatment groups at 8 weeks. After that time, serum T levels were not significantly elevated throughout the remainder of the treatment period in the finasteride group. There was little change in serum T levels after week 26 in the dutasteride group. Shigehara et al[6,7] reported that dutasteride treatment for 12 months significantly increased total T and free T values with mean rates of 20.9% ± 30.1% (range 53% to 88%) and 27.4% ± 62.7% (range 68% to 391%), respectively. It should be noted that within the same study 42 patients (55%) had an increase >20% in total T value, whereas 45% had a smaller increase (<20%) or a decrease in total serum T values, further raising the concern that such increases cannot be explained by increased testicular function or a novel endocrine-dependent mechanism. In summary, we found no evidence that directly supports the suggestion that 5α-RIs promote increased testicular de novo steroid biosynthesis.

2. Is the increase in T levels associated with finasteride or dutasteride therapy due to increased secretion of gonadotropins (LH and FSH)?

1 potential mechanism to explain the reported increases in serum T levels is the activation of the feedback mechanisms involving the hypothalamic–pituitary–gonadal axis (HPGA) by which reduction in 5α-DHT levels stimulates LH release resulting in increased testicular T biosynthesis. For this to be true, one would expect a concomitant increase in gonadotropin levels with increased serum T concentrations.

In 1990, Gormley et al[21] reported on the gonadotropin response to finasteride use in a blinded placebo-controlled study of various doses of finasteride compared with placebo. The study consisted of initial dosing of 25, 50, or 100 mg of finasteride followed by a second period of reduced finasteride doses of either 0.04-, 0.12-, 0.2-, or 1-mg doses. Significant decreases in 5α-DHT were reported for all groups and increases in serum T were reported for all dosages ≥1 mg. No significant changes in gonadotropins were observed in any group at any time point. 2 years later, Gormley et al[1] reported on the biochemical responses of 895 men to 1 or 5 mg of finasteride and placebo after 12 months of treatment. In this study, serum LH was increased at 2 months in the placebo group as well as both treatment groups. The finasteride group demonstrated significantly higher increases in LH levels than placebo ($P < .05$). In the 5-mg finasteride group, serum LH increased from 6.6 mIU/mL (±2.6) at baseline to 7.4 mIU/mL (±2.7) at 2 months and to 7.6 mIU/mL (±2.9) at 12 months. Serum T values increased by 8% to 10% in the finasteride treated group. The absolute magnitude of the LH increase was modest at 1.0 mIU/mL, which may explain the increases in serum T concentrations reported in this study.

Table 3. Characteristics and outcomes of studies included in the meta-analysis

Study	Subjects, n	Age range, y	Clinical condition	Drug	Dose	Duration	Comments
Gormley et al, 1992[a,1]	297	40–83	BPH	Finasteride	5 mg	12 mo	Serum T levels were significantly higher in the treated subjects.
Gormley et al, 1992[b,1]	298	40–83	BPH	Finasteride	1 mg	12 mo	Serum T levels were significantly higher in the treated subjects.
Uygur et al, 1998[20]	48	49–81	BPH	Finasteride	5 mg	3–6 mo	T levels increased by 15% after treatment.
Denti et al, 2000[42]	16	55–74	BPH	Finasteride	5 mg	6 mo	No significant changes in serum T were found.
Matsumoto et al, 2002[23]	75	46–76	BPH	Finasteride	5 mg	4–48 mo	Serum T levels were significantly higher in the treated subjects.
Clark et al, 2004[a,27]	57	≥50	BPH	Finasteride	5 mg	6 mo	T levels increased by 10% after treatment.
Clark et al, 2004[b,27]	57	≥50	BPH	Dutasteride	0.5 mg	6 mo	T levels increased by 21% after treatment.
Amory et al, 2007[a,50]	34	18–55	Healthy men	Finasteride	5 mg	12 mo	Finasteride transiently increased serum T.
Amory et al, 2007[b,50]	33	18–55	Healthy men	Dutasteride	0.5 mg	12 mo	Dutasteride transiently increased serum T.
Stanczyk et al, 2013[28]	27	57–79	Men with PSA ≥4 ng/mL	Finasteride	5 mg	12 mo	Serum T was increased by 21% in the treated group after 12 months.
Upreti et al, 2014[a,25]	16	20–85	Healthy & BPH	Finasteride	5 mg	3 mo	Significant changes in serum T were reported.
Upreti et al, 2014[b,25]	16	20–85	Healthy & BPH	Dutasteride	0.5 mg	3 mo	No significant changes in serum T were reported.
Traish et al, 2015[15]	470	47–68	BPH	Finasteride	5 mg	36 mo	Significant decreases in serum T levels were recorded.
Traish et al, 2017[35]	230	52–72	BPH	Dutasteride	0.5 mg	36 mo	Significant decreases in serum T levels were recorded.
Maeda et al, 2018[5]	110	NR	BPH	Dutasteride	0.5 mg	3 mo	T levels increased by 16.8% after treatment.

BHP = benign prostatic hyperplasia; NR = not reported; PSA = prostate-specific antigen; T = testosterone.

In a recent study, Maeda et al[5] reported mean LH levels after dutasteride treatment were approximately 20% higher than those at baseline. Andriole et al[48] reported that during 2 years on finasteride, serum T levels increased 20%, serum LH increased 25%, and FSH increased by about 15%. However, Roberts et al[49] showed small but significant increases in serum T (mean increase of 18.3% ± 3.1%, 19.4% ± 3.6%, and 18.1% ± 3.6% for the 5-, 1-, and 0.2-mg finasteride groups, respectively, at month 6; $P < .01$ vs placebo). These small increases in serum T were not associated with significant changes in serum LH or FSH from baseline.

In 2004, Clark et al[27] reported on 399 men treated with either finasteride (5-mg dose) or dutasteride (0.01-, 0.05-, 0.5-, 2.5-, or 5.0-mg doses). After 24 weeks, the small increases in LH levels were not significantly different from placebo. Increases of 0.2 mIU/mL (±1.4) were noted in the finasteride treated group and 0.3 mIU/mL (±2.7) in the dutasteride group compared with a small decrease in the placebo group of 0.9 mIU/mL (±1.4). The authors reported more complete 5α-DHT suppression in the dutasteride group (98.4% mean reduction) vs the finasteride group (70.8% mean reduction). There were no statistically significant changes in LH levels.

Matzkin et al[36,37] randomized 23 men with BPH to either placebo or 1 mg of finasteride daily or 5 mg of finasteride daily and demonstrated no significant change in LH (baseline 7.9 mIU/mL ±1.8 to 8.8 mIU/mL ± 2.9) or FSH (baseline 10.9 nIU/mL ± 2.6 to 17.4 mIU/mL ± 6.2 IU/mL) in subjects treated with 5 mg of finasteride over the course of 12 months. In addition, whereas 5α-DHT levels did show predictable suppression, mean serum T levels were not significantly altered at any time point. Amory et al[50] reported no significant changes for serum gonadotropins, E_2, or SHBG.

Even more confusing are the results reported by Uygur et al.[20] In this study 48 men (mean age 63 years) with symptoms of BPH were administered 5 mg of finasteride daily for 6 weeks. The authors observed a 24% decrease in FSH and a 16% decrease in LH at 6 months despite an increase in serum T by 15%. 5α-DHT levels were decreased by 60%. There is no

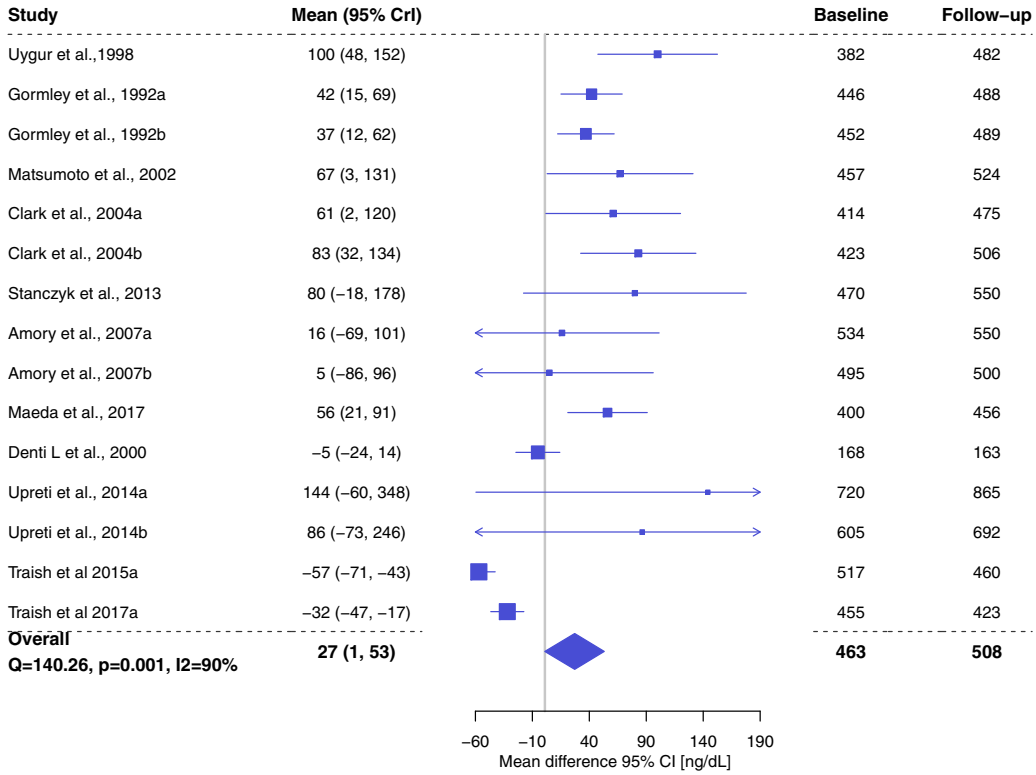


Figure 5. Bayesian meta-analysis of baseline change in T levels after treatment with finasteride or dutasteride.

known mechanism to support reduction in LH spurring the synthesis of androgen under this treatment condition.

Rittmaster et al[51] treated 20 healthy men with 5 mg of finasteride or placebo for 28 days. Finasteride-treated men demonstrated a modest rise in mean serum T levels at 14 days (18.3 nmol/L from 17.6 nmol/L) that did not persist at day 28. At no point was there any significant change in gonadotropin levels in the treated group. Fruzzetti et al[44] treated 10 women

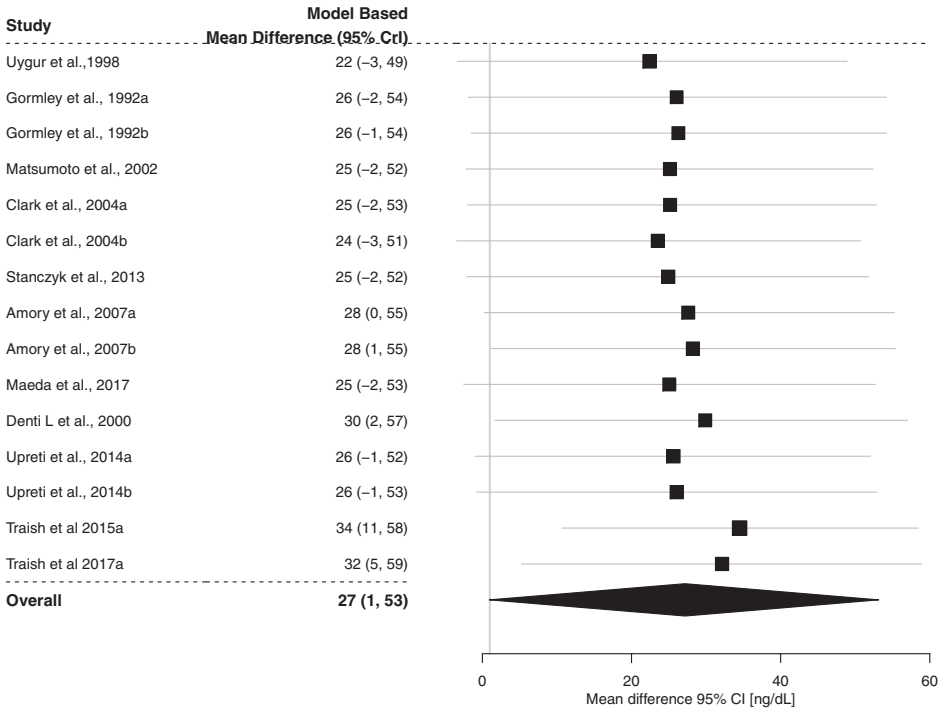
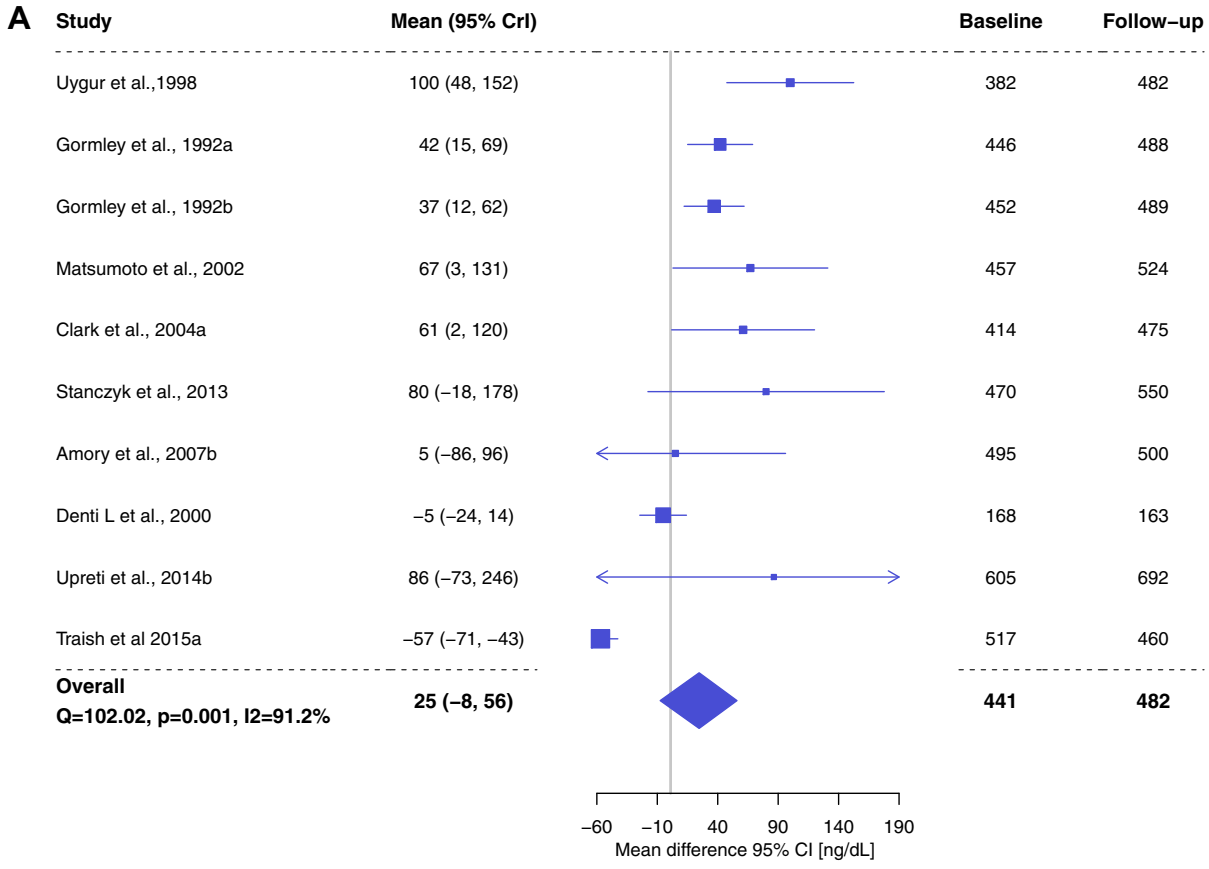


Figure 6. Sensitivity analysis of all studies assessing influence of each included study on meta-analysis results for the association of treatment with finasteride or dutasteride and baseline change in T levels.



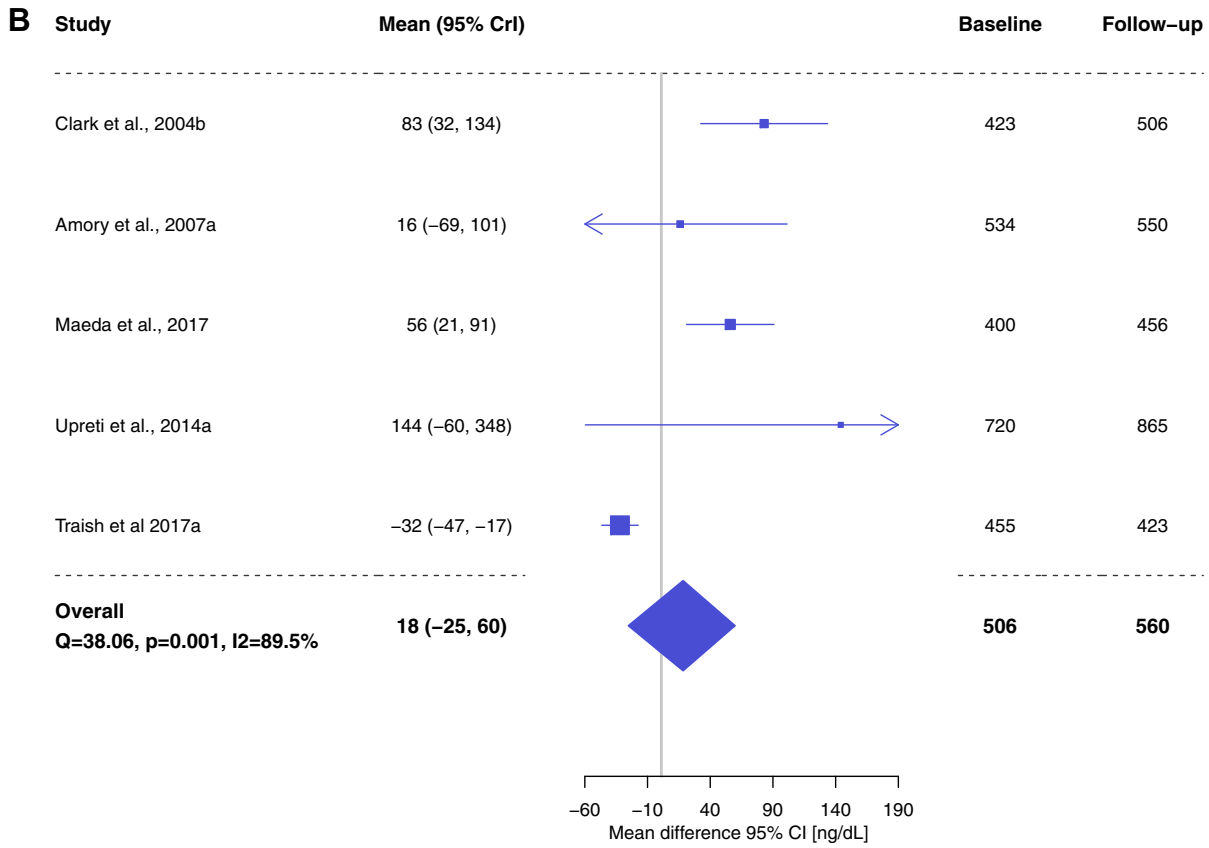


Figure 7. A Bayesian meta-analysis of baseline change in T levels associated treatment with finasteride. B Bayesian meta-analysis of baseline change in T levels after treatment with dutasteride.

with hirsutism with 5 mg of finasteride daily for 3 months and demonstrated no changes in LH pulsatility. Serum T levels were increased compared with baseline at 3 months, however, there was no placebo group.

It should be noted that limited basic and clinical research evidence exist to support a hypothesis that 5α-RIs stimulate T synthesis via increased gonadotropin release. Prahalada et al[52,53] demonstrated in mice models that 5α-RIs administration led to Leydig cell hyperplasia in 52% of treated mice compared with 24% of controls. The authors then explored whether an increase in LH could explain Leydig cell changes. A statistically significant increase in serum LH was found in finasteride-treated mice leading the authors to hypothesize that 5α-DHT is involved in the regulation of LH release in mice.

Castro-Magna et al[17] examined serum gonadotropin levels in 22 men (ages 16 to 30 years) with male pattern baldness treated with 10 mg of finasteride for 2 years. A significant rise in E_2 and T concentrations and a significant decrease in 5α-DHT were observed. However, no significant gonadotropin change was reported after 2 years of treatment. Serum T at baseline was 17.2 nmol/L (±2.5) and increased to 26.3 nmol/L (±1.7) and 5α-DHT levels reduced from 1.45 nmol/L to 0.38 nmol/L (±0.10). Similarly, Schwartz et al[18,19] randomized patients to either placebo, 5 mg of finasteride, or varying dosages of MK-386. The higher doses of dutasteride (50 mg) demonstrated a 16.5% decrease in serum LH from baseline of −1.2 mIU/mL. The authors reported this was likely due to chance, given the small numbers and the fact the LH increased by 16% in the placebo group, which would bias the results toward significance despite a modest absolute change in LH.

Bayram et al[54] treated 35 hirsute women with finasteride to explore improvements in hirsutism score. No changes were seen in LH/FSH at 3, 6, or 12 months. However, SHBG values did increase from baseline 33.7 ± 14.9 to 42.6 ±15.7 by 12 months ($P < .05$). A review of the available literature (Table 4) showed no consistent rise in gonadotropins in response to 5α-RIs therapy in men and suggest that such mechanism is not supported based on a robust, large-scale human trials demonstrating no significant increase in LH, which may explain that any perceived increase in serum T may not be attributed to feedback mechanism that regulate de novo T biosynthesis. In summary, 5α-RIs use was associated in some studies, but not all, with a modest increase in LH concentrations, and this rise did not consistently parallel observed increases in serum T concentrations. It is therefore uncertain to what extent, if any, a rise in gonadotrophins explains observed increases in serum T with 5α-RIs use.

3. Can the reported increase in T levels associated with finasteride or dutasteride therapy be explained by reduced conversion of T to 5α-DHT?

It has been postulated that the reported increase in circulating T levels are a result of reduction in conversion of T to 5α-DHT; thus, more T remains unconverted to its reduced derivative and would contribute to increased serum T levels. Although this explanation is plausible, the stoichiometry of this pathway does not account fully for the reported increases in serum T levels, because the increase in serum T levels often exceed those accounted for by the reductions in serum 5α-DHT levels, on molar equivalency bases (Table 5). Debruyne et al[55] reported that T levels in men receiving placebo were 3,959 pg/mL at baseline and 3,990 and 4,718 pg/mL at 24 and 48 months, respectively. In men treated with dutasteride T levels were 4,049 pg/mL at baseline and 4,797, and 4,904 pg/mL at 24 and 48 months, respectively. 5α-DHT levels in the placebo arm were 407 pg/mL at baseline and 427 pg/mL at 24 months. Men treated with dutasteride had 5α-DHT levels of 424, 39, and 31 pg/mL at baseline, 24, and 48 months, respectively. Thus, the reduction in 5α-DHT levels, on molar bases, did not account for the reported increases in serum T levels, based on chemical stoichiometry.

As shown in Table 5 the reduction in serum 5α-DHT in response to finasteride or dutasteride therapy ranged between 1 and 1.6 nM. In a simple model where reductions in conversion of T to 5α-DHT would result in increased serum T by a similar amount, this would yield an increased serum T by 1 to 1.6 nM, or the equivalent of 30 to 47 ng/dL. The increases reported in T levels range from 1.3 to 5.3 nM (40 to 155 ng/dL), with considerable variability among different reported studies. It is conceivable that the observed increase in T concentrations are, in part, the result of inhibition of T conversion to 5α-DHT.

Matsumoto et al[23] reported that mean baseline T levels in the placebo group and in the finasteride treated group were 495 and 427 ng/dL, respectively, and after finasteride these were 494 ng/dL and 497 ng/dL, respectively. The mean increase in serum T with finasteride was therefore 23%. Mean 5α-DHT concentrations declined with finasteride from 40 ng/dL to 11.3 ng/dL. In the same report, Matsumoto et al[23] showed similar changes in serum T and 5α-DHT concentrations with finasteride, approximately 30 ng/dL decline in 5α-DHT and 70 ng/dL rise in T. Because the molecular weights of T and 5α-DHT are similar, the stoichiometry would suggest that if the decline in 5α-DHT accounted entirely for the rise in T concentrations, the magnitude of the change for one should be equivalent to the change in the other. However, they are not. The increase in T concentrations is more than double the decline in 5α-DHT concentration. It appears that the rise in serum T cannot be solely explained by reductions in the conversion of T to 5α-DHT alone, as previously reported[56–60]

4. Are increases in serum T levels due to increases in SHBG synthesis?

One could postulate that a significant change in SHBG levels, due to 5α-RIs therapy, may explain the reported increases in serum T values because SHBG-bound testosterone is

metabolized and cleared at a lower rate than free T. However, the available data do not support this possibility. Denti et al[42] reported on 28 men treated with 5 mg of finasteride and found no change in SHBG concentration at 3 or 6 months. Free T and E_2 concentrations also remained unchanged. Bayram et al[54] treated 35 hirsute women with 5 mg of finasteride to explore improvements in hirsutism score. SHBG values increased from baseline 33.7 ± 14.9 to 42.6 ± 15.7 at 12 months ($P < .05$). E_2 levels were also significantly increased at 12 months. In another study, Bayram et al[61] randomized 56 hirsute women to either 2.5 or 5 mg of finasteride daily for 12 months. In this study, serum SHBG and gonadotropins did not change significantly. Interestingly, mean E_2 concentrations increased from 61.8 pg/mL to 94.0 pg/mL. There was no associated rise in serum T values. Although the evidence regarding the influence of 5α-RI on SHBG is limited, the few available studies fail to indicate a consistent effect on SHBG concentrations, and this mechanism appears unlikely to contribute to the rise in serum T with 5α-RIs treatment.

5. Is the reported increase in serum T due to increased availability of SHBG binding sites from reduced 5α-DHT-SHBG binding?

1 final possibility to be considered is whether the greatly reduced serum concentration of 5α-DHT, with presumably reduced SHBG-5α-DHT binding, means that there are additional SHBG binding sites for T from vacated 5α-DHT binding. Because T metabolism and clearance rates may be significantly reduced by SHBG trapping, this could account for an increase in serum T.

Circulating 5α-DHT values are approximately 7% to 10% of that of total serum T values.[62] Yet due to higher binding affinity of 5α-DHT to SHBG compared with T, almost 60% of 5α-DHT is SHBG-bound compared with approximately 45% of T. The binding affinity of 5α-DHT to SHBG is 2- to 3-fold higher than for T, with an equilibrium dissociation constant, Kd ∼ 0.18×10^{-9}M for 5α-DHT and 0.625×10^{-9}M for T.[63] It may be reasonably expected that reduction in circulating 5α-DHT would result in vacated binding sites on SHBG. These unoccupied binding sites would then become available for circulating T molecules, with binding reducing the rate of T metabolism and clearance (Figures 8 A and B). This dynamic may be a plausible mechanism by which the observed increases in T in men with low baseline T levels receiving 5α-RIs therapy may be explained.[5,8,23] In summary, it is plausible that the observed increase in T levels, in men treated with finasteride or dutasteride, reflects re-equilibration of T with SHBG as a response to dissociation of 5α-DHT from SHBG.

Re-equilibration of T with unsaturated SHBG may represent the mechanism underlying the increases in serum T in populations with lower baseline T values and not in men with higher baseline T concentrations. Because T and 5α-DHT compete for SHBG binding sites, the relative proportions of bound T and 5α-DHT will differ based on their serum concentrations, with more bound T versus 5α-DHT in men with higher serum T concentrations compared with men with lower T and a similar 5α-DHT concentration. Loss of 5α-DHT would therefore open up a greater number of additional binding sites for an individual with baseline low T, resulting in a higher percentage increase in total T.

Although we are not aware of any relevant experimental data to either support or contradict this hypothesis, we propose a simple experimental approach to test the hypothesis. Baseline total and free T as well as SHBG concentrations are determined in a group of men prior to treatment with finasteride or dutasteride. Occupied (bound) and unoccupied (free) fractions of SHBG are determined by ligand binding assays. Based on baseline total T levels, men with low baseline T levels are assigned to group A. Men with high baseline total T levels are assigned to group B. Both groups will be treated with 5 mg of finasteride for ≥3 months. Total T and free T levels and occupied and unoccupied SHBG binding sites will be determined at 3 months. We hypothesize that total T concentrations will increase in group A concomitant with increased fraction of occupied SHBG and reduction in the unoccupied fraction of SHBG. We also expect that free T will remain unchanged or reduced in this group. In group B, we expect that there will be minimal changes in the total T, free T and the occupied and unoccupied fractions of SHBG.

DISCUSSION

In this article, we reviewed the findings from published reports regarding the impact of 5α-RI treatment on serum testosterone concentrations, and also performed a meta-analysis. Several studies reported a modest (10% to 20%) increase in total serum T concentrations compared with baseline T levels (Table 1). Several other studies reported no increase in serum T concentrations (Table 2). 11 studies met criteria for a meta-analysis, which revealed no significant increase in serum T concentrations in response to 5α-RIs therapy for periods ≥3 months (Figures 5, 6, and 7). Considerable variability was observed among studies analyzed, with differences involving study design, drug, dosages, durations of follow-up, and population characteristics. A number of studies that reported results qualitatively are listed in Table 2 but did not provide adequate quantitative data to be included in the meta-analysis. Given these limitations, one cannot exclude the possibility that the failure to observe a significant increase in serum T with 5α-RI use in this analysis may be attributed, in part, to heterogeneity of the included studies.

We have examined several possible mechanisms that might explain a small rise in serum T. We found no credible evidence to suggest that finasteride or dutasteride increases testicular de novo T biosynthesis. In a recent review by Voznesensky et al,[64] it was reported that in men with BPH treated with finasteride, the drug-related adverse events profile remained independent of

Table 4. Studies demonstrating no changes in LH levels in response to finasteride or dutasteride treatment

Study	Subjects, n	Age range, y	Drug	Dose	Treatment duration	Authors' comments on the effects on LH and FSH levels
Gormley et al, 1990[21]	42 30	19–46 40–77	Finasteride	25, 50, and 100 mg or 0.04–1 mg	11 d 14 d	At baseline, mean serum LH levels ranged from 4.2–4.8 IU/L, and serum FSH levels ranged from 2.0–3.2 IU/L. No significant change from baseline occurred in any treatment group.
Gormley et al, 1992[1]	895	40–83	Finasteride	1 and 5 mg	12 mo	Serum LH increased in all 3 groups during the first 2 months. The increases in the finasteride group were significantly higher than those in the placebo group ($P < .05$).
Matzkin et al, 1992[36]	23	58–79	Finasteride	5 mg	1–12 mo	There were no significant differences in the LH baseline levels between the different treatment groups ($P = .92$ and $P = .34$, respectively). No significant change from baseline values occurred in any treatment group.
Castro-Magna et al, 1996[17]	22	16–30	Finasteride	10 mg	2 y	No significant changes were observed in gonadotropin secretion.
Schwartz et al, 1997[19]	20	18–45	MK-386	0.1, 0.5, 5, 20, and 50 mg	14 d	The percentage changes in LH from baseline after 2 weeks of treatment for the 20- and 50-mg MK-386 and placebo treatments were 16.2% ± 10.2%, 216.5% ±11.1%, and 16.3% ± 11.0%, respectively ($P < .05$ for 50 mg MK-386 vs placebo). These differences probably reflect a chance observation and are unlikely to be clinically meaningful; however, this remains to be confirmed in future investigations.
Uygur et al, 1998[20]	48	49–81	Finasteride	5 mg	3–6 mo	FSH and LH levels decreased by 24% and 16%, respectively. The changes in the serum levels of these hormones were further evident at month 6.
Clark et al, 2004[27]	399	>50	Finasteride Dutasteride	5 mg of finasteride Once-daily dosing of dutasteride (0.01, 0.05, 0.5, 2.5, or 5 mg)	24 wk	Observed were small increases of 0.2 1.4 mIU/mL for finasteride, which were not significantly different from placebo. Observed were small increases of 0.3 2.7 mIU/mL for dutasteride at 0.5 mg, which were not significantly different from placebo.
Amory et al, 2007[50]	99	18–55	Dutasteride/Finasteride	0.5 mg/5 mg	12 mo	No significant increases in LH or FSH were reported with either finasteride or dutasteride.
Maeda et al, 2018[5]	110	NR	Dutasteride	0.5 mg	3 mo	Significant increases in LH were reported.

FSH = follicle-stimulating hormone; LH = luteinizing hormone; NR = not reported.

Table 5. Reported changes in T and 5α-DHT levels in men treated with finasteride or dutasteride

Study	T (nmol/L)	*P* Values	5α-DHT (nmol/L)	*P* Values	Reduction in 5α-DHT (nmol/L)	Increase in T (nmol/L)
Debruyne et al, 2004[55]						
Placebo						
Baseline	12.46		1.4			
24 mo	12.55		1.46			
48 mo	14.48					
Dutasteride						
Baseline	12.74		1.458			
24 mo	14.04		0.134		−1.324	1.33
48 mo	15.43		0.106		−1.352	2.69
Stanczyk et al, 2013[28]						
Placebo						
Baseline	17.67		1.728			
1 mo	18.369	.1828	1.728	.9519		
3 mo	17.67	.9071	1.615	.5415		
6 mo	18.76	.2584	1.683	.9749		
12 mo	16.29	.1448	1.615	.0126		
Finasteride						
Baseline	16.29		1.890			
1 mo	19.755	.002	0.378	<.0001	−1.512	3.465
3 mo	19.06	.003	0.378	<.0001	−1.512	2.77
6 mo	18.71	.0033	0.378	<.0001	−1.512	2.42
12 mo	19.06	.0015	0.412	<.0001	−1.478	2.77
Uygur et al, 1998[20]						
Baseline	13.24		1.487			
3 mo of finasteride	15.38	.015	0.983	.0001	−0.504	2.14
6 mo of finasteride	16.70	.005	0.371	.0001	−1.116	3.46
Clark et al, 2004[27]						
Baseline	14.319		1.291			
24 wk of dutasteride	16.458	<.05	0.404	<.001	−0.887	2.139
Gormley et al, 1990[21]						
Baseline	22.7		2.19			
Day 11	22.7		2.05			
12.5 mg of finasteride (0 time)	21.6		2.2			
Day 11	23.8		0.63		−1.57	2.2
50 mg of finasteride (0 time)	21.3		1.98			
Day 11	26.5	<.01	0.63		−1.35	5.2
50 mg of finasteride twice daily (0 time)	21.6		2.02			
Day 11	26.9	<.01	0.44		−1.58	5.3
Matsumoto et al, 2002[23]						
BMD subset						
Baseline (placebo)	17.16		1.64			
Mean after 4 y (placebo)	17.14		1.75			
Baseline (finasteride)	14.80		1.385			
Mean after 4 y (finasteride)	17.25		0.388		−0.997	2.45
PLESS Cohort						
Baseline (placebo)	14.42		1.533			
Mean after 4 y (placebo)	14.98		1.499			
Baseline (finasteride)	15.835		1.56			
Mean after 4 y (finasteride)	18.155		0.40		−1.16	2.32
Upreti et al, 2014[25]						
Before finasteride	21.0		2.1			
After finasteride	24		1	<.01	−1.1	3.0

DHT = dihydrotestosterone; T = testosterone.

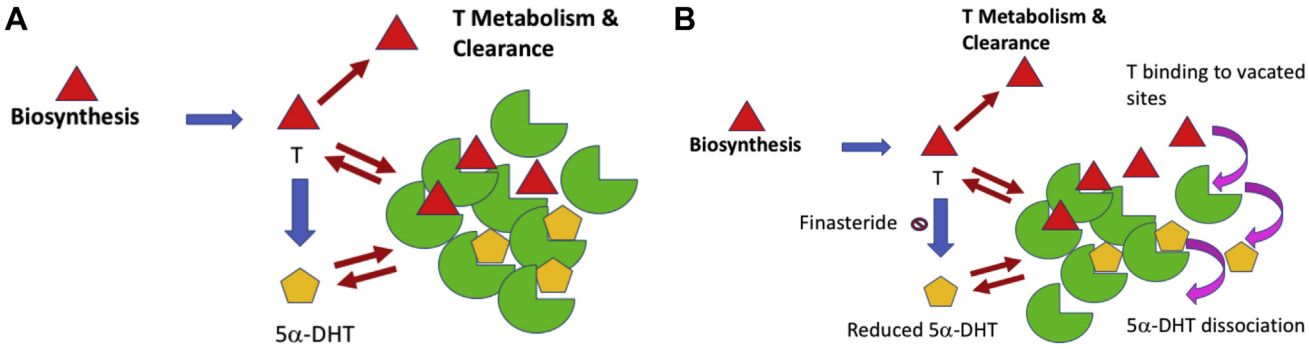


Figure 8. A, B Alternative explanation for the observed T increase above baseline in men treated with finasteride or dutasteride. Panel A depicts equilibrium binding established between SHBG and free T and free 5α-DHT. Because 5α-DHT has a higher affinity for SHBG, a larger fraction of 5α-DHT is bound to SHBG. Panel B depicts inhibition of 5α-R reduces 5α-DHT levels resulting in dissociation of the 5α-DHT-SHBG complex into free SHBG and 5α-DHT. The vacated SHBG binding sites permit binding of T to SHBG, shifting the equilibrium in favor of T binding.

normal physiological T levels, suggesting that finasteride treatment did not produce significant changes in serum T levels. This supports our contention that 5α-RIs do not increase serum T levels. The possibility that 5α-RIs may increase serum T via increased gonadotropin concentrations also appears unlikely, as studies failed to demonstrate a consistent pattern of increased LH or FSH concentrations. There are also no data to support the possibility that 5α-RIs raise serum T by increasing SHBG concentrations. 1 mechanism that may contribute in part is that serum T rises because less of it has been enzymatically converted to 5α-DHT. At best, this mechanism may account for less than half of the observed changes in serum T, in those studies where an increase in serum T occurred.

At this time, we believe the most compelling mechanism is replacement of vacated 5α-DHT binding sites on SHBG by T. A key observation is that increases in serum T were noted mainly in men with low baseline T levels and not in men with higher baseline T levels (Figures 2 and 3).[5,8,24] Because T and 5α-DHT bind to SHBG with high affinity, we believe that finasteride inhibition of 5α-R isozymes with concomitant reduction in conversion of T to 5α-DHT results in reduced circulating 5α-DHT and dissociation of bound 5α-DHT from SHBG, thus vacating more steroid binding sites on SHBG (Figure 8). These unoccupied binding sites on SHBG permit re-establishing of new equilibrium between T and SHBG and sequestering more T molecules, thus reducing T metabolism and clearance from the plasma. In men with low baseline T levels (<330 ng/dL), the SHBG binding isotherm is unsaturated with T and 5α-DHT, and any reductions in 5α-DHT levels, due to finasteride, contribute to vacating a fraction of the available SHBG binding sites, therefore permitting a new equilibrium to be re-established between T and SHBG. In men with high baseline T levels (>550 ng/dL), however, the SHBG binding isotherm is nearly saturated with T and 5α-DHT and reductions in 5α-DHT levels, due to finasteride or dutasteride, constitute a small fraction of the available binding sites. Therefore, the newly established equilibrium between T and SHBG accounts for a very small fraction of bound T, and this may in part explain why no significant increase in total serum T is observed in men with high baseline T levels (Figures 2 and 3).

CONCLUSION

In summary, 5α-RI therapy is not associated with consistent and significant increases in serum T levels. Men with low serum T concentrations may have a greater likelihood of experiencing a rise in serum T with 5α-RI treatment. Based on the very modest increase in serum T in those studies where such a rise was observed, it is unlikely that this change is clinically meaningful. We advance the hypothesis that the rise in serum T in response to 5α-RI therapy, when it occurs, results from re-equilibration of SHBG binding to T, as serum concentrations of 5α-DHT decline.

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