ORIGINAL RESEARCH—ENDOCRINOLOGY

Male Sexual Function Can Be Maintained Without Aromatization: Randomized Placebo-Controlled Trial of Dihydrotestosterone (DHT) in Healthy, Older Men for 24 Months

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ABSTRACT

Introduction. Male sexual function is highly androgen dependent but whether aromatization of testosterone (T) to estradiol is required remains contentious.
Aim. This study aims to investigate the effects of selective estrogen deficiency induced by a nonaromatizable androgen, dihydrotestosterone (DHT), on sexual function of healthy middle-aged and older men.
Methods. Randomized clinical trial of daily transdermal DHT (70 mg) or placebo gel treatment in 114 healthy middle-aged and older (>50 years, mean 60.5 years) men without known prostate disease maintaining selective estrogen deficiency for 24 months.
Outcome Measures and Analysis. The end points were responses to a psychosexual and mood questionnaire completed before, at 3 months, then at 6 monthly intervals during and 3 months after study. Data were analyzed by mixed model analysis of variance for repeated measures using age and body mass index (BMI) as covariates and including interactions of treatment with age and time-on-study.
Results. DHT treatment increased serum DHT with complete suppression of serum T, luteinizing hormone, follicle stimulating hormone, and estradiol throughout the 24-month study resulting in reduced spinal bone density. There were no spontaneous complaints, or discontinuations for, adverse effects on sexual function during the study. DHT administration had no effects on any of 33 measures of sexual function and mood, apart from a mild, but significant decrease in overall sexual desire, which was reversible after cessation of treatment. Increasing age and less often increasing BMI were associated with significant decreases in most aspects of sexual function.
Conclusions. We conclude that aromatization plays only a minimal role in maintenance of sexual function in healthy eugonadal middle-aged or older men, but age and obesity are significantly associated with decreases in most aspects of self-reported sexual function and satisfaction. The dependence of male sexual function on aromatization may be conditional on age and obesity and can be overcome by a nonaromatizable androgen. **Sartorius GA, Ly LP, and Handelsman DJ. Male sexual function can be maintained without aromatization: Randomized placebo-controlled trial of dihydrotestosterone (DHT) in healthy, older men for 24 months. J Sex Med 2014;11:2562–2570.**

Key Words. Androgen; Testosterone; DHT; Aromatization; Aromatase; Sexual Function; Obesity; Age; Men

Introduction

Psychosexual function is important to reproductive and general health of men. An inexorable decline in male sexual function is a relatively early and frequent feature of male aging. This strongly motivates finding therapeutic relief constituting a major health-seeking behavior in the community. Although it is well established that adequate androgen exposure is indispensable for development and maintenance of optimal male sexual function, the mechanism and threshold of

this androgen effect remains contentious. Testosterone (T) plays its major role in the initiation of sexual behavior, notably through effects on libido and arousal, whereas later neurovascular effects, such as erectile and ejaculatory function, appear less androgen but more age dependent. In men with organic androgen deficiency due to recognized pathology of the hypothalamo–pituitary testicular axis, T restores sexual function in a rapid and effective manner [1] when blood T drops below men's individually distinct blood thresholds [2]. By contrast, among men without pathologically based androgen deficiency including those with erectile dysfunction or andropause, T administration has no beneficial effects exceeding the placebo effects of expectation [3,4]. Although it is known that T's bioactive metabolites, estradiol acting via estrogen receptors and dihydrotestosterone (DHT) acting via the androgen receptor, are involved in maintenance of sexual and other androgenic function, the balance varies between tissues and remains not fully understood [5].

Recent evidence from a study of selective estrogen deficiency induced by pharmacological blockade of estradiol synthesis demonstrates a partial reduction in male sexual function despite maintaining eugonadal circulating T concentration [6]. The ensuing interpretation that aromatization is important to male sexual function predicts that selective estrogen deficiency produced by other means would also fail to maintain male sexual function.

Aims

Our previous placebo-controlled study of high-dose DHT administration that produced marked, selective estrogen deficiency for 24 months [7] provides a unique opportunity to evaluate the impact of sustained estrogen deficiency on male sexual function while androgen exposure was maintained. Therefore, we undertook this secondary analysis of sexual function and mood in healthy middle-aged and older eugonadal men using validated patient-reported psychosexual and mood questionnaires as outcome measures. The original study was designed to investigate the hypothesis that a nonamplifiable androgen may reduce midlife prostate growth rate in asymptomatic male volunteers without known prostate disease. Daily DHT gel treatment for 24 months did not reduce prostate growth rate but did cause a mild decrease in spinal but not hip bone density.

Materials and Methods

Study Design

The study was a randomized, placebo-controlled, double-blind, parallel-group clinical trial of daily transdermal treatment with DHT (70 mg, Andractim, Besins, Montrouge, France) or matching placebo gel over 24 months conducted at a single center, the Andrology Department, Concord Hospital, a third-party referral center and teaching hospital in Sydney, Australia, with details published previously [7]. Briefly, men aged 50 years or older without known prostate disease were recruited by advertising with exclusions for severe chronic medical or mental disease requiring medication, polycythemia, a history of drug abuse, addiction, hypogonadism, or use of disallowed medication that interfered with sex steroid action or bone mass. From 309 volunteers screened by telephone interview, 114 men were randomized to DHT (n = 56, with 37 completing full study) or placebo (n = 58, with 44 completing full study) gel. Visits were scheduled at baseline and then at 3, 6, 12, 18, and 24 months during treatment and 3 months after (recovery) cessation of treatment. Adverse effects caused withdrawal for protocol-specified reasons (eight polycythemia and three increased prostate specific antigen) all in DHT group but none were symptomatic nor had prostate cancer. Other withdrawals were unrelated to DHT administration (overall, nine withdrew consent, two protocol deviations, one lost to follow-up, three nonadherence). Volunteers provided written informed consent but received no payments or reimbursements. The study had an independent data safety and monitoring board and was registered (ACTRN12605000358640) and approved by the Sydney South West Area Health Service Human Ethics Committee within NHMRC Guidelines for Human Experimentation. The study sponsor (BHR Pharma) did not influence study design, data analysis, interpretation, or publication, which were solely the responsibility of the investigators.

Main Outcome Measures

At every visit, participants were asked for any spontaneous complaints of adverse effects or events. They completed the validated University of California, Los Angeles psychosexual diary [8], a self-report instrument for evaluating sexual function and mood in hypogonadal and eugonadal men, using a temporal framework of the last week prior to the clinic visit and covering the domains: sexual desire, enjoyment with or without partners,

Table 1 Serum estradiol (pg/mL) measured by liquid chromatography, tandem mass spectrometry at different time-points (months 0, 6, 12, 18, 24 and at recovery 3 month posttreatment visit) during the study in the two treatment groups (DHT and placebo)

Time (months)	Baseline	6	12	18	24	Recovery
DHT	16.5 ± 1.6	2.2 ± 0.7	1.4 ± 0.6	1.4 ± 0.5	1.8 ± 0.6	11.9 ± 1.5
Placebo	15.9 ± 1.4	14.0 ± 1.1	16.7 ± 1.2	17.0 ± 1.3	17.4 ± 1.6	15.3 ± 1.4

activities, performance, and satisfaction as well as positive and negative mood. Scores for sexual desire and enjoyment with or without a partner ranged from 0 to 7 on a Likert-type scale. Sexual performance included assessment of satisfaction with erection on a 0–7 Likert scale and percent erection from 10% to 100%. Sexual activity was rated according to 12 items (sexual daydreams, anticipation of sex, sexual interactions with partner, flirting by participant or by others toward participant, ejaculation, orgasm, intercourse, masturbation, spontaneous erections during night, spontaneous erections during day, erection in response to sexual activity) scored according to a yes/no format with the sum of positive answers recorded for this domain. Two questions were also added from the Brief Male Sexual Inventory about sexual satisfaction [9]. Mood was evaluated according to four positive (alert, full of life/energetic, friendly, and well/good) and five negative mood responses (angry, irritable, sad or blue, tired, and nervous) each scored on a 0–7 Likert scale. In addition, summary of positive and negative scores were calculated.

Serum T, DHT, and estradiol (E2) were measured by liquid chromatograph and tandem mass spectometry [10], whereas LH and FSH were measured using automated immunoassays [7].

Data Analysis

Data were analyzed according to an intention-to-treat including all participants who attended the first visit 1, used at least 1 dose of study medication and completed at least two questionnaires. Data were analyzed using NCSS version 9 (NCSS LLC, Kaysville, UT, USA) by applying a linear mixed model analysis for repeated measures with main effect being treatment (DHT vs. placebo) and estimating covariate effects of age, obesity (body mass index [BMI]) together with age × treatment and time-on-study × treatment interactions. The linear model was fitted by restricted maximum likelihood using the Newton-Raphson search algorithm and fitting autoregressive variance model allowing for different time estimates.

Results

The DHT and placebo treated groups were well matched for baseline characteristics, discontinuations for other than protocol-specified reasons and there was a high compliance with medication [7]. The hormonal effects reported previously were, briefly, serum DHT concentration was increased ~10-fold over baseline, remaining stable during ongoing treatment and returned to pretreatment baseline 3 months after end of treatment. Serum estradiol (Table 1), T, LH, and FSH were suppressed by DHT treatment and returned to baseline after end of treatment but were unchanged by placebo treatment. Mean serum E_2 concentration during DHT treatment was 1.7 ± 0.3 (standard error of the mean) pg/mL. Spinal, but not hip, bone density was significantly reduced by DHT vs. placebo treatment. These findings were consistent with sustained, marked estrogen deficiency in the presence of a maintained androgen exposure (Figure 1).

Sexual Function

DHT treatment had no significant effect on any of 13 measured aspects of sexual function or mood other than on overall sexual desire. For overall sexual desire, DHT treatment produced a mild decrease that was fully reversed after cessation of treatment ($P = 0.030$; $P = 0.036$, age × treatment interaction $P = 0.036$), with significant negative effects of age ($P < 0.0001$) and BMI ($P = 0.003$). Scaled according to the pretreatment between-subject baseline standard deviation (SD), the effect size of DHT treatment was –0.06 SD units. By contrast, the effects of age were more prominent among younger men with the effect size, evaluated at the three quartiles of age, of –0.25 SD units at 55 years of age, –0.06 SD units at 60 years of age, and +0.22 SD units at 65 years of age. Adding an age × BMI interaction into the analysis rendered nonsignificant both main effects of age and BMI (Figure 2).

Age was associated with reduced sexual function for 17 of 20 measures of sexual function but

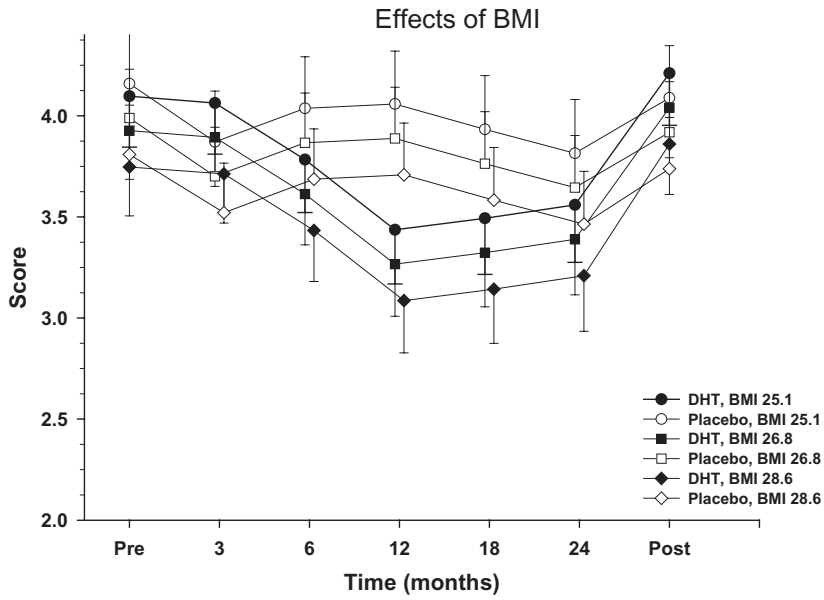

Figure 1 Mean and standard error of the mean for Likert score on overall sexual desire for men treated with DHT (filled symbols) or placebo (open symbols) evaluated at 1st (age 55 years, circles), 2nd (median, age 60 years, squares), and 3rd (age 65 years, diamonds) quartiles of age before, during, and after the study.

not for three (sexual interactions with a partner, consider lack of sex drive to be a problem, or overall satisfaction with sex life). In nine of these 17 measures, BMI was also associated with an adverse effect on sexual function (overall sexual desire, enjoyment with partner, erection in response to sexual activity, spontaneous nocturnal erections, anticipation of sex, ejaculation, % of full erection, and summation of positive sexual function responses), in another eight, the effects of age were not accompanied by significant effects of BMI (enjoyment without partner, spontaneous daytime erections, sexual daydreams, flirting by self or by others, orgasm, intercourse, and masturbation). For the three responses where age was no significant, BMI was associated with significantly lower sexual function in two but not the other (sexual interaction with partner). Generally, when both age and BMI were significant as main effects, the addition of an age × BMI

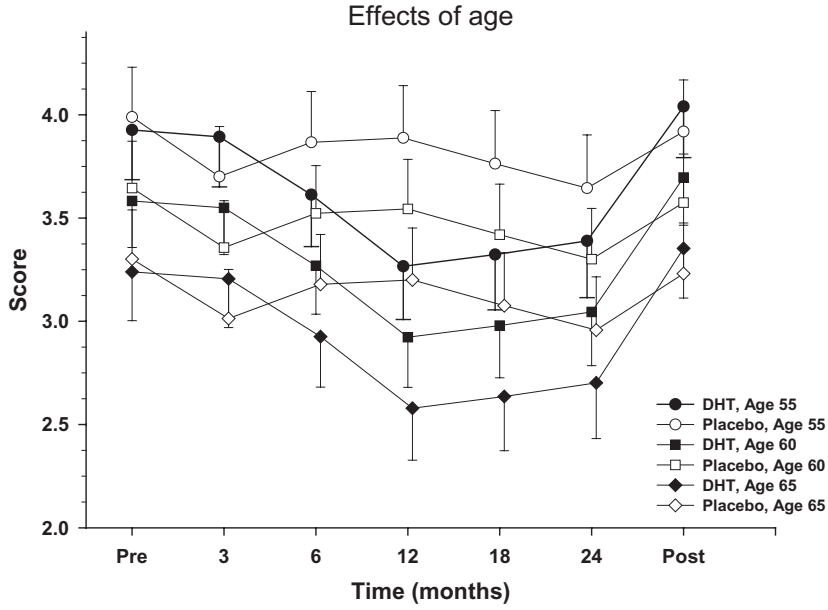

Figure 2 Mean and standard error of the mean for Likert score on overall sexual desire for men treated with DHT (filled symbols) or placebo (open symbols) evaluated at 1st (BMI 25.1 kg/m^2, circles), 2nd (median, BMI 26.8 kg/m^2, squares), and 3rd (BMI 28.6 kg/m^2, diamonds) quartiles of BMI before, during, and after the study.

interaction term rendered both no longer statistically significant as main effects.

Mood

DHT treatment had no significant effect on any mood variable. Age was associated with negative effects on four responses (angry, irritable, sad or blue, and nervous), whereas BMI was associated with negative effects on three responses (alert, full of life/energetic, and well/good) while for two other mood responses neither age nor BMI were significantly associated (tired and friendly). The summary of negative responses was significantly associated with age but not BMI, whereas the summary of positive responses was negatively associated with BMI but not age.

Discussion and Conclusions

Sexual function involves both objective biological mechanisms together with unobservable subjective components, the latter only verifiable through self-report. For men, sexual activity is initiated through subjective motivational impulses that culminate in the mechanical neurovascular effector mechanisms. Within this framework, mature male sexual function requires achieving a threshold of adequate androgen exposure commencing during puberty and subsequently permissive androgen effect to maintain sexual function during adult life, whereas castration in late adult life has reduces but does not abolish male sexual function [11–14]. The nature and mechanism of such permissive androgenic maintenance of mature male sexual function remain difficult to study, which requires reliance on self-report together with the clinical research tools of placebo, blinding, and randomization, so they remain ill-defined.

The present study reveals that, in middle-aged and older eugonadal men in good health, sustained estrogen deficiency for 24 months induced by administration of the nonaromatizable androgen DHT has no major detrimental effects on self-reported sexual function or mood, apart from a minor, reversible reduction in overall sexual desire. The effect on sexual desire is small in magnitude, being only detectable using a powerful study design, but was not sufficient for participants, unpaid volunteers, to notice or complain of. This overall negative finding contrasts with another recent study of selective estrogen deficiency created by administering an aromatase inhibitor (anastrozole) to healthy young men while maintaining stable eugonadal circulating T concentrations that reported a partial reduction in sexual function [6]. The following key differences in study design may explain this apparent discrepancy.

Age is an important design difference in that men in the present study were older (mean 60 years vs. 33 years [6]) and, as we observed that older age was associated with reduced male sexual function, this age difference is likely to have influenced the different findings. As increasing BMI is correlated with advancing male age, the association of higher BMI with reduced sexual function may be a surrogate for age [15]. Another age-related factor may be progressive accumulation of underlying cardiovascular disease, a comorbidity of aging with principal impact on erectile function [16] as a sentinel feature [17]. Additionally, although less plausible, a role of different background androgen exposure from the relatively high single DHT dose vs. graded doses of T in the previous study cannot be fully excluded.

Another design differences between the studies is how estrogen deficiency was produced. The previous study induced medical castration with add-back of graded doses of T for all participants. Participants were then divided into two nonrandomized cohorts, one without and the other with, administration of a single dose of anastrozole. The nonrandomized design for the aromatase inhibition means that nonspecific, off-target drug side effects could be confounded with pharmacological effects and therefore drug side effects cannot be excluded to explain partially impaired sexual function.

A further design differences is in the psychosexual function instruments used to characterize sexual function. The previous study used a quality of life instrument for men castrated for advanced prostate cancer [18] comprising three responses for sexual interest and three for sexual activity, each averaged to create two summary variables; however, its responsiveness to castration or less extreme hormonal perturbations has not been reported. By contrast, the scales used in the present study, comprising 20 responses for sexual function and nine for mood, were developed and validated in studies of hypogonadal men treated with T [8,9].

An important issue for studies of the impact of selective estrogen deficiency is the degree of estrogen deficiency. The efficacy of aromatase inhibitors in men is questionable in that among 17 studies over a range of doses (modal dose 1 mg daily, range 0.5 mg daily to 80 mg over 5 days) and duration of

treatment (5 days to 12 months), the magnitude of lowering in serum E_2 was <50% (Supporting Information Table S1) raising the possibility that pharmacological inhibition of estrogen synthesis may be suboptimal. However, most studies (n = 9) used invalid direct (unextracted) E_2 immunoassays [19], although other studies used more reliable indirect (using extraction and chromatography) immunoassays (n = 6, five from a single center) as well as mass spectrometry (n = 1) and in vitro bioassay (n = 1). Although reported serum E_2 concentrations measured by mass spectrometry (MS) appeared to be comparable between studies, both had a high proportion of samples with undetectable serum E_2 concentrations assigned an arbitrary low concentrations (as indicated by mean serum E_2 concentrations below limits of quantitation) so that more sensitive analysis of left censored data would be required to verify whether the degree of suppression was comparable [20]. Furthermore, based on the affinity of estrogen receptors for estradiol, it is likely that serum E_2 levels <1 pg mL may be biologically effective [21], consistent with evidence that, in subprimates, circulating serum E_2 levels are undetectable under most physiological conditions by even the most sensitive MS-based methods [22].

Salient experimental data on the estrogen requirement for male sexual function comes from genetic mouse models of aromatase or estrogen receptor knockouts that abolish specific steps in a hormonal mechanism more effectively and unequivocally than pharmacological blockade. Different aromatase knockout models display variable impairment of male fertility ranging from near normal [23] to markedly reduced with the fertility deficit due mainly to reduced, but not abolished, male sexual behaviors [24]. A similar phenotype of reduced but not abolished male sexual behavior is evident in estrogen receptor α, but not β, knockouts [25–28]. Such phenotypes are, however, influenced by both genetic background and environmental conditions [29,30].

There is significant corroborative evidence that administration of nonaromatizable androgens such as DHT, nandrolone, or mesterolone may improve or at least not impair male sexual function. For example, in studies of sexual function, oral DHT undecanoate treatment of agonadal men maintains sexual function for 9 weeks [31], whereas sexual function was also improved more than placebo with daily DHT gel administration for 6 months to men with andropause symptoms and serum T <15 nmol/L [32]. Among studies of at least 1 month duration where adverse effects on sexual function may have led to discontinuations, no spontaneous complaints were reported in placebo-controlled studies of 1 [33] or 3 [34] months duration, a crossover study of 1 month duration [35] as well as uncontrolled studies of 5 months [36] or 3 months [37] duration. Similar observations apply to nandrolone, another potent androgen that is minimally or not aromatized in vitro [38] or in vivo [39,40]. When administered to men with HIV and weight loss, nandrolone improved sexual function more than placebo [41], whereas other placebo-controlled studies of nandrolone administration of at least 1 month duration reported no spontaneous complaints of adverse effects on sexual function [42–44]. Similar effects are reported with a nandrolone analog, 7α methyl nandrolone [45]. Furthermore, the widespread illicit abuse of nandrolone by bodybuilders is not accompanied by complaints of sexual dysfunction. Finally, administration of 100 mg mesterolone, an oral DHT analog, daily for 4 weeks improves sexual function of hypogonadal men [46]. In the latter double-blind study although mesterolone was less effective than 120 mg oral T undecanoate, mesterolone effects may have been underestimated in the absence of a known dose-response for mesterolone through possibly using a suboptimal dose.

Furthermore, the aromatization hypothesis that male sexual function is estrogen dependent predicts that estrogen receptor blockade may be detrimental to male sexual function. However, estrogen receptor blockers such as clomiphene, tamoxifen, raloxifene, or other mixed estrogen receptor agonist/antagonists have long been used off-label to treat men complaining of andropause, gynecomastia, infertility, and androgen abuse-induced hypogonadism. Although there are no specific studies of male sexual function, the best available evidence suggests that antiestrogen treatment does not impair male sexual function [47–53].

The strengths of this study include its randomized, placebo-controlled, double-blind design, use of appropriate validated sexual function questionnaires, and the prolonged duration of DHT-induced selective estrogen deficiency in otherwise healthy middle-aged and older men. The study's limitations include that sexual function can only be determined by unverifiable subjective self-report. However, any recall bias due to this unavoidable limitation of evaluating self-reported sexual function was minimized by prospective administration of validated questionnaires using a brief time window of reference. Another limitation of a sec-

ondary analysis is that the study was not powered for this specific psychosexual end point, although they were planned secondary outcomes. Nevertheless, the study was sensitive enough to detect a subclinical effects on reduced overall sexual desire. The older age group may be both a strength and a limitation. Although it corresponds better to the population of aging men seeking treatment for failing sexual function, we were unable to directly test the hypothesis of estrogen dependence of male sexual function in younger men to formally replicate the previous study using a different mode of inducing selective estrogen deficiency. It may be speculated that the change in estrogen dependency of male sexual function with age may represent a form of neural plasticity following age-dependent changes in neuroendocrine regulation of male sexual function [54,55]. We conclude that aromatization of T may not play an essential role in human male sexuality and that age and obesity may be more powerful determinants of male sexual function than aromatization, which may be more important in younger men.

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(a) Drafting the Article
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(b) Revising It for Intellectual Content
Gideon A. Sartorius; Lam P. Ly; David J. Handelsman

Category 3

(a) Final Approval of the Completed Article
Gideon A. Sartorius; Lam P. Ly; David J. Handelsman

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Effects of anastrozole in suppressing serum estradiol concentrations: summary of 17 studies involving 289 men.