SEXUAL MEDICINE REVIEWS

Alternatives to Testosterone Therapy: A Review

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ABSTRACT

Introduction: Although testosterone therapy (TTh) is an effective treatment for hypogonadism, recent concerns regarding its safety have been raised. In 2015, the US Food and Drug Administration issued a warning about potential cardiovascular risks resulting from TTh. Fertility preservation is another reason to search for viable alternative therapies to conventional TTh, and in this review we evaluate the literature examining these alternatives.

Aims: To review the role and limitations of non-testosterone treatments for hypogonadism.

Methods: A literature search was conducted using PubMed to identify relevant studies examining medical and non-medical alternatives to TTh. Search terms included *hypogonadism, testosterone replacement therapy, testosterone therapy, testosterone replacement alternatives, diet and exercise and testosterone, varicocele repair and testosterone, stress reduction and testosterone,* and *sleep apnea and testosterone*.

Main Outcome Measures: Review of peer-reviewed literature.

Results: Medical therapies examined include human chorionic gonadotropins, aromatase inhibitors, and selective estrogen receptor modulators. Non-drug therapies that are reviewed include lifestyle modifications including diet and exercise, improvements in sleep, decreasing stress, and varicocele repair. The high prevalence of obesity and metabolic syndrome in the United States suggests that disease modification could represent a viable treatment approach for affected men with hypogonadism.

Conclusions: These alternatives to TTh can increase testosterone levels and should be considered before TTh. **Lo EM, Rodriguez KM, Pastuszak AW, Khera M. Alternatives to Testosterone Therapy: A Review. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Testosterone; Aromatase Inhibitors; Selective Estrogen Receptor Modulator; Varicocele; Testosterone Therapy; Human Chorionic Gonadotropin

INTRODUCTION

Testosterone affects numerous physiologic processes including sexual function, secondary sex characteristics, lean body mass, insulin resistance, lipid parameters, bone density, and the immune system.[1–3] The 2010 Endocrine Society guidelines define hypogonadism in men as "a clinical syndrome that results from the failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis."[4] Male hypogonadism presents with low serum testosterone levels and symptoms that can include decreased libido, erectile dysfunction, loss of vitality, loss of lean muscle mass, fatigue, and depression.[3] Prepubertal hypogonadism can lead to small genitalia and difficulty gaining muscle mass. In older men, hypogonadism can manifest through decreased libido, depression, and decreased muscle mass and can result in decreased bone mineral density and increased cardiovascular risk.[4,5] The European Male Aging Study (EMAS) proposed that criteria for a diagnosis of late-onset hypogonadism include the presence of at least 3 sexual symptoms, total testosterone levels lower than 11 nmol/L, and free testosterone levels lower than 220 pmol/L.[6] Harman et al[7] classified hypogonadism differently, defining it as a visit in which circulating testosterone is lower than 325 ng/dL or the free testosterone index is less than 1.53 nmol/nmol (2.5th percentile for men 21–45 years of age in their study). Using their criteria, the prevalence of androgen deficiency in men 20 to 45 years of age is approximately 3% to 8%. However, the incidence of hypogonadism increases with

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age, reaching approximately 20% in men older than 60 years, 30% in men older than 70 years, and 50% in men older than 80 years. In addition, the Massachusetts Male Aging Study estimated that approximately 2.4 million 40- to 69-year-old men in the United States have androgen deficiency and concluded that the rate increased significantly with age.[8]

Treatment with exogenous testosterone has demonstrated efficacy in the management of hypogonadism. Testosterone therapy (TTh) can improve sexual function, muscle strength and bone density, and mood and cognition.[9] Although these benefits can significantly improve the quality of life for hypogonadal men, TTh has some side effects. The most common dose-limiting side effect of TTh is erythrocytosis, which can be managed by decreasing the dose or therapeutic phlebotomy.[10,11] Other common side effects of TTh include male infertility, testicular atrophy, and gynecomastia.[12–14] Given the androgen-responsive nature of prostate cancer, there also is concern that exogenous testosterone might drive prostate cancer growth, although this has not been demonstrated to date.[3,15] TTh also has been suggested to increase the risk for venous thromboembolism, but this also has not been rigorously proved.[11,16] The relation between TTh and cardiovascular risks also remains incompletely determined.[17] Nevertheless in 2015, the US Food and Drug Administration (FDA) issued a warning cautioning that testosterone might increase the risk of heart attack and stroke.[18]

Although TTh is effective in ameliorating hypogonadal symptoms, many patients seek alternatives that can preserve fertility and testicular volume and delay the onset to which they would need to take TTh. Concerns regarding lifelong commitment to TTh can drive patients and physicians to seek alternatives, and the medical and natural alternatives to TTh are the focus of this review. A literature search was conducted using PubMed to identify relevant studies examining medical and non-medical alternatives to TTh. Search terms included *hypogonadism, testosterone replacement therapy, testosterone therapy, testosterone replacement alternatives, diet and exercise and testosterone, varicocele repair and testosterone, stress reduction and testosterone,* and *sleep apnea and testosterone.*

ALTERNATIVES TO TESTOSTERONE THERAPY

Medical Therapies

Medical alternatives to TTh include drugs that can increase serum testosterone levels indirectly and include FDA-approved treatments such as human chorionic gonadotropin (hCG) and off-label alternatives that include aromatase inhibitors (AIs) such as anastrozole and letrozole and selective estrogen receptor modulators (SERMs) such as clomiphene citrate (Table 1, Figure 1).

Human Chorionic Gonadotrophin

hCG is a placental homologue of luteinizing hormone (LH) derived from the urine of pregnant women or produced in vitro using recombinant DNA technology.[19] Because of its similarity to LH, hCG can stimulate testosterone production by testicular Leydig cells. Vicari et al[20] retrospectively examined 17 men with isolated hypogonadotropic hypogonadism who received hCG 1,500 IU 3 times a week. Men were grouped into a small testis subset (testicular volume < 4 mL) and large testis subset (testicular volume ≥ 4 mL). The 2 groups demonstrated significant increases in plasma testosterone levels, with the small testis and large testis groups initially starting with basal testosterone levels of 0.05 and 0.5 ± 0.05 ng/mL respectively, and increasing to 5.5 ± 0.4 and 7.6 ± 1.3 ng/mL, respectively, after 24 months of hCG treatment. Kim et al[21] found similar results when administering hCG 1,500 to 2,000 IU 3 times a week for 8 weeks to 20 men with hypogonadotropic hypogonadism. When comparing baseline with 24 weeks after treatment, they found

Table 1. Medical therapies

Treatment	Studies	Findings
hCG	Vicari et al, 2012	24-mo hCG treatment significantly increased testosterone levels
	Kim et al, 2011	Significant increase in serum testosterone levels 24 wk after 8-wk hCG treatment regimen
AIs (anastrozole, letrozole)	Leder et al, 2004	Significant increase in serum testosterone levels after 12 wk of anastrazole treatment
	T'Sjoen et al, 2005	Significant increase in testosterone levels compared with placebo after 28 d of letrozole
	Dias et al, 2016	Significant increase in serum testosterone levels compared with controls after 3, 6, and 12 mo of anastrazole therapy
SERMs (clomiphene)	Katz et al, 2011	Significant increase in total testosterone levels after 19 mo of clomiphene treatment
	Shabsigh et al, 2005	Significant increase in testosterone levels after 4–6 wk of clomiphene treatment
	Guay et al, 2003	Significant increase in free testosterone levels after 4 mo of clomiphene treatment

AIs = aromatase inhibitors; hCG = human chorionic gonadotropin; SERMs = selective estrogen reuptake modulators.