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 2018;6:106–113.**

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

Received April 30, 2017. Accepted September 24, 2017.

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https://doi.org/10.1016/j.sxmr.2017.09.004

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.

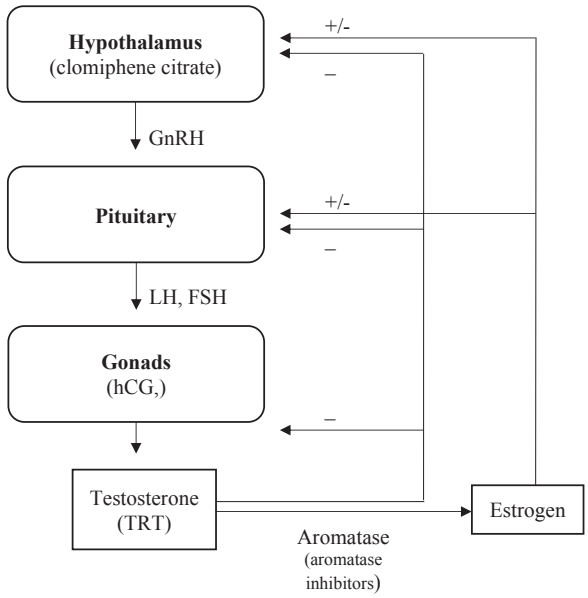

Figure 1. Targets of action for medical therapies on hypothalamic-pituitary-gonadal axis. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; TRT = testosterone replacement therapy.

significant increases in mean serum testosterone levels from 0.90 ± 1.35 to 5.58 ± 1.75 ng/mL ($P < .05$). Neither study directly addressed the effects of hCG on symptoms associated with hypogonadism as determined by the EMAS (decreased sexual interest and morning erections and erectile dysfunction) but Vicari et al did specify that 10 of their patients with hypogonadotropic hypogonadism desired to impregnate their partners, and 7 achieved this. Although testosterone alone inhibits spermatogenesis, hCG can stimulate spermatogenesis given its direct positive effects on the testis and can be used in lieu of or as an adjunct treatment to TTh to simulate or maintain spermatogenesis.[22–24] Thus, in men with secondary hypogonadism, particularly those who wish to preserve fertility and/or testicular size, hCG treatment should be considered. For those presenting with infertility presumably resulting from TTh, recent studies have shown that hCG can stimulate recovery of spermatogenesis.[24] Risks and complications to consider are headaches and fatigue. Data supporting the long-term safety of hCG treatment are currently lacking.

Aromatase Inhibitors

AIs block the conversion of testosterone to estradiol by inhibiting the aromatase enzyme, consequently lowering estradiol levels and limiting the negative feedback of estradiol on the hypothalamic-pituitary-gonadal axis. This action can directly and indirectly increase serum testosterone levels. Inhibition of aromatase increases gonadotropin-releasing hormone, LH, and follicle-stimulating hormone levels, subsequently increasing serum testosterone levels.[25] The use of AIs in men with hypogonadism is currently considered off-label. In 2004, Leder et al[26] conducted a randomized controlled trial examining 37 elderly men with serum testosterone levels lower than 350 ng/dL and found that administration of anastrozole 1 mg/day or 1 mg twice weekly significantly increased serum testosterone levels after 12 weeks. In men taking 1 mg/day, serum testosterone levels increased from 343 ± 61 to 572 ± 139 ng/dL, and in men taking 1 mg twice weekly, serum testosterone levels increased from 397 ± 106 to 520 ± 91 ng/dL ($P < .01$ vs placebo for the 2 groups). In a similar study in 2005, T'Sjoen et al[25] compared letrozole 2.5 mg/day with placebo in healthy young (22–30 years old) and elderly (68–81 years old) men. After 28 days of treatment, they found that young and elderly men taking letrozole, but not placebo, had significantly increased testosterone levels (by 146% and 99%, respectively; $P < .001$ for the 2 groups). More recently in 2016, Dias et al[27] conducted a placebo-controlled study to evaluate the effect of anastrazole 1 mg/day on serum testosterone levels and found that testosterone levels increased significantly in the AI group compared with controls after 3, 6, and 12 months of therapy. Regarding symptoms associated with hypogonadism, Leder et al[26] found no significant differences in erectile function (International Index of Erectile Function) between the AI and placebo groups. Common side effects reported with the use of AIs include hot flashes, weight gain, insomnia, and joint aches.[28] AIs also have been associated with decreased bone mineral density, likely owing to their suppressive effects on estrogen levels.[29] Nevertheless, the ability of AIs to significantly increase serum testosterone levels men of all ages and their oral bioavailability make them an attractive alternative to TTh.

Selective Estrogen Receptor Modulators

SERMs act as estrogen receptor antagonists and agonists depending on the tissue. Clomiphene citrate (clomiphene) is a SERM that acts as an estrogen antagonist in the hypothalamus and pituitary gland. By preventing the inhibitory effects of estrogen on gonadotropin production, clomiphene stimulates LH and follicle-stimulating hormone secretion, which can stimulate the spermatogenic and steroidogenic functions of the testes.[19,30] Clomiphene is used off-label in men with hypogonadism. A 2011 prospective study by Katz et al[31] examined 86 men 22 to 37 years old with testosterone levels lower than 300 ng/dL. Patients received clomiphene 25 to 50 mg every other day and attended follow-up after a mean of 19 months on therapy. Total testosterone levels increased from a baseline of 192 ± 87 to 485 ± 165 ng/dL (mean ± SD; $P < .01$). Shabsigh et al[32] prospectively followed 36 Caucasian men with hypogonadism who were administered clomiphene 25 mg/day. Follow-up visits after 4 to 6 weeks showed mean testosterone levels increasing from 247.6 ± 39.8 ng/dL before treatment to 610.0 ± 178.6 ng/dL after treatment ($P < .00001$). In addition, they observed an increase in the ratio of testosterone to estrogen from 8.7 to 14.2 ($P < .001$). Guay et al[33] evaluated the effect of a 4-month course of clomiphene 50 mg orally on Monday, Wednesday, and Friday

on 228 men with hypogonadotropic hypogonadism and erectile dysfunction. Of the initial 228 men, 173 completed the 4-month regimen, with significant increases in free testosterone levels from 9.3 to 21.2 pg/mL ($P < .001$). Efficacy studies have found that clomiphene is generally tolerable, with only mild symptoms such as headache, dizziness, and fatigue recorded as side effects.[34] Clomiphene dosing often begins with a lower dose (25 mg/day or 50 mg every other day) and then progresses to higher doses (50 mg/day), if necessary, in part because some patients have decreased motile sperm counts while on high dosages (100 mg 3 times/week) that resolves after decreasing the dose.

When properly dosed, clomiphene citrate can be considered an effective and safe alternative to TTh.

Non-Drug Therapies to Increase Testosterone Levels

According to a 2015 study by Maseroli et al,[35] approximately 65% of patients with non-classic secondary hypogonadism have at least 1 of the following 3 conditions: diabetes mellitus, metabolic syndrome (MetS), and obesity. These patients might have adult-onset hypogonadism.[36] This syndrome is clinically distinct from classic primary and secondary hypogonadism and often occurs in men with chronic medical conditions that are common in aging men, making it difficult to separate the comorbidities from the influence of aging.[37,38]

For several conditions associated with adult-onset hypogonadism (obesity, diabetes, hypertension, and hyperlipidemia), initial treatment starts with disease modification. The approach to treating hypogonadism should be the same and many natural alternatives to TTh provide a vehicle for this. In addition to disease modification, other non-drug therapies include improvements in sleep, decreasing stress, and varicocele repair (Table 2).

Diet, Exercise, and Weight Loss

Chronic health conditions such as obesity and MetS are associated with decreased serum testosterone levels. Obesity correlates with more rapid decreases in testosterone levels with increasing age.[39] In 2006, Corona et al[40] examined 236 men with MetS and found a linear relation between the severity of MetS and testosterone levels. Specifically, circulating total testosterone decreased as the number of MetS components (high blood pressure, high fasting glucose, increased waist circumference, decrease high-density lipoprotein cholesterol, and increase triglycerides) increased. This relation between hypogonadism and MetS is bidirectional: men with hypogonadism also are more likely to have elements of MetS. Corona et al also found that patients with MetS demonstrate high levels of somatized anxiety, which also can play a role in sexual function.

These associations between obesity and MetS raise the question of whether lifestyle changes to decrease fat mass and other MetS components could consequently increase testosterone levels.[41] Even without reversing MetS, exercise and diet modification can increase serum testosterone levels. Kumagai et al[42] conducted a randomized controlled trial in 44 obese men and found that a 12-week lifestyle modification program involving

Table 2. Non-drug therapies

Treatment	Studies	Findings
Diet, exercise, and weight loss	Kumagai et al, 2015	12-wk lifestyle modification program involving aerobic exercise and diet modification significantly increased mean testosterone levels
	Heufelder et al, 2009	52-wk program of diet and exercise significantly increased mean serum testosterone levels
	Camacho et al, 2013	Individuals who lost ≥10% of weight between visits showed a significant increase in testosterone levels
	Corona et al, 2013	Weight loss through low-calorie diets or bariatric surgery was associated with significant increases in total testosterone levels
Improvements in sleep	Santamaria et al, 1998	Men with OSA treated with UPPP had significant 3-mo postoperative increases in testosterone levels
	Leproult and Van Cauter, 2011	Restriction of sleep to 5 h/night decreased testosterone levels by 10–15%
Stress reduction	Singer and Zumoff, 1992	Men with high stress levels had significantly lower serum testosterone levels compared with controls
	Guay et al, 2010	Men with higher work stress had higher than expected incidence of hypogonadism
Varicocele repair	Su et al, 1995	Varicocelectomy significantly increased mean testosterone levels
	Tanrikut et al, 2011	Varicocele repair significantly increased testosterone levels
	Sathya Srini and Belur Veerachari, 2011	Significantly increased total testosterone levels were found at 12-mo follow-up after varicocelectomy
	Li et al, 2012	Mean serum total testosterone significantly increased after varicocelectomy

OSA = obstructive sleep apnea; UPPP = uvulopalatopharyngoplasty.

aerobic exercise 3 times per week and a diet limited to 1,680 kcal/day increased mean testosterone levels from 12.3 ± 0.9 to 13.2 ± 1.1 nmol/L ($P < .05$). Although the study by Kumagai et al demonstrates an important improvement for obese individuals, it leaves unanswered a follow-up question of whether these lifestyle changes would have any effect on patients with normal body mass indices.

A study by Heufelder et al[43] of 32 men with hypogonadism, MetS, and type 2 diabetes mellitus similarly showed significantly improved serum testosterone levels after a 52-week program of diet and exercise as instructed by dietitians and physiotherapists. Mean serum testosterone concentrations increased significantly from 10.4 ± 0.2 to 11.2 ± 0.2 nmol/L. Furthermore, 31.3% of patients were considered to have recovered from MetS, as diagnosed using Adult Treatment Panel III criteria (≥3 of the following 5 criteria being met: waist circumference > 40 inches in men or > 35 inches in women; blood pressure > 130/85 mm Hg; fasting triglyceride level > 150 mg/dL; fasting high-density lipoprotein cholesterol level < 40 mg/dL in men or < 50 mg/dL in women; fasting blood sugar > 100 mg/dL), at the end of the 52-week period. The finding of recovery from MetS in approximately 1 third of patients and a mean increase in testosterone across all patients supports the likelihood that these 2 components are likely linked, although an important factor to keep in mind regarding the study of Heufelder et al is the absence of an actively treated placebo group.

A randomized controlled trial by Camacho et al[44] in 2013 examined the effects of weight change and lifestyle factors on hypothalamic-pituitary-gonadal axis function in middle-age and older men and found similar results. 2,736 men 40 to 79 years old were surveyed and paired testosterone data were acquired for 2,395 patients. Camacho et al observed that those who lost at least 10% of weight (n = 83) between visits showed an increase of 2.9 nmol/L (85 ng/dL) in testosterone levels ($P < 0.01$). These 2 studies support lifestyle modifications resulting in weight loss as positive influences on serum testosterone levels.

In the absence of exercise, decreased weight is associated with significant increases in testosterone levels. In 2013, Corona et al[45] performed a meta-analysis and review of 13 studies evaluating the effect of a low-calorie diet and 11 studies looking at the role of bariatric surgery on serum testosterone levels and found that weight loss achieved through diet or bariatric surgery was associated with significant increases in total testosterone levels ($P < .0001$). Regarding specific diets, Mediterranean diet patterns (high intake of low-fat dairy, eggs, poultry, fish, vegetables) have demonstrated a positive association with total sperm count. Western diet patterns (high consumption of vegetable oils, high-fat dairy, processed meat, refined grains) were found to demonstrate an inverse relation with sperm concentration, although this was restricted to overweight or obese men.[46]

Many products on the market are marketed as "natural testosterone boosters." These are not regulated by the FDA and their risks cannot be discussed at length because of a lack of objective studies to define efficacy and safety. With any supplement, there is the concern that there are variabilities in ingredient quantities, that active ingredients might interfere with other prescribed drugs, and that the supplement itself might be toxic.

Lifestyle modification such as aerobic exercise and diet resulting in weight loss provide a relatively risk-free approach to increase testosterone levels and should generally be recommended as a first-line, drug-free approach in overweight men. Bariatric surgery, which also can lead to weight loss, also can be considered in men who desire to avoid a potentially lifelong commitment to medication.

Improvements in Sleep

Men with obstructive sleep apnea (OSA) have lower serum testosterone levels, possibly because of nocturnal hypoxia and blunting of LH levels.[47] In 1998 Santamaria et al[48] conducted a prospective controlled trial of 12 men with OSA treated with uvulopalatopharyngoplasty and observed that 3-month postoperative testosterone levels increased from 13.31 ± 1.07 to 16.59 ± 0.72 nmol/L ($P < .02$), a 95-ng/dL improvement in addition to improvements in OSA symptoms. Although Santamaria et al found that uvulopalatopharyngoplasty treatment for OSA could increase testosterone levels, their study was limited by a relatively small sample and, unfortunately, other OSA treatments might not have a similar impact on testosterone levels. For example, continuous positive airway pressure alleviated OSA symptoms but failed to produce significant improvements in testosterone levels in 2 studies.[49,50]

Duration of sleep also is associated with lower serum testosterone levels. In 2011, Leproult and Van Cauter[51] reported that sleep deprivation (restriction of sleep to 5 hours a night) decreased testosterone levels by 10% to 15%. Other studies have argued that timing of sleep is important when considering the effects of restricted sleep hours on testosterone because of its circadian variability. Reynolds et al[52] found that when sleep was restricted during the first half of the night and permitted from 4:00 to 8:00 AM for 5 nights in a row, no significant change in testosterone were observed.

Thus, improvements in sleep quality and duration also can positively affect serum testosterone levels and can provide an additional medication-free alternative to TTh. In hypogonadal men with OSA, certain improvement of sleep quality can increase testosterone levels. For men with poor sleep habits, restructuring sleep schedules to allow longer sleep duration, or sleep at optimal times, also can improve testosterone levels.

Decreasing Stress

Previous studies have found a negative relation between cortisol and testosterone levels. One theory to explain this association is that cortisol disrupts the steroidogenic process in testicular Leydig cells through an inhibitory enzymatic mechanism.[53] The association between low testosterone and stress suggests that stress management could offer another lifestyle

modification that can increase testosterone levels. Singer and Zumoff[54] found that men with high stress levels had significantly lower serum testosterone levels compared with controls. They evaluated 7 internal medicine residents (stressed) who had a mean serum testosterone level of 11.8 ± 1.06 nmol/L, significantly lower than testosterone levels of non-physician male health care personnel (controls; 20.6 ± 5.28 nmol/L; $P <$ .0005). More recently, in 2010 Guay et al[55] examined the associations between hypogonadism (total testosterone < 300 ng/dL) and chronic conditions including diabetes mellitus, anxiety and depression, hypertension, and hyperlipidemia. They found that men with higher work stress had a higher than expected incidence of hypogonadism (42.6%). Men with significant work stress typically worked more than 50 to 60 hours per week, sometimes held more than 1 job, had long commutes, and often were forced to meet deadlines or quotas.

Thus, amelioration of stress and optimization of work-life balance might further improve testosterone levels without needing medical therapy. However, it is important to note that a strong association between stress and testosterone levels remains to be defined.

Varicocele Repair

Varicocele repair can offer a unique approach to improving testosterone levels for a subset of hypogonadal men. Current theory contends that the pathophysiology of varicoceles might impair Leydig cell activity, resulting in lower serum testosterone levels.[56] In a retrospective review of 53 infertile men, Su et al[57] found that varicocelectomy increased mean testosterone levels from 319 ± 12 to 409 ± 23 ng/dL ($P <$ .0004). More recently, Tanrikut et al[58] conducted a case-control study and found that varicocele repair significantly increased testosterone levels (358 ± 126 ng/dL at baseline to 454 ± 168 ng/dL after repair; $P <$ .001). Similar studies have reinforced these claims. Sathya Srini and Belur Veerachari [59] conducted a prospective study examining 200 men with varicocele associated with infertility and with a serum testosterone level lower than 280 ng/dL. Men were split into 2 groups of 100, with one group receiving microsurgical varicocelectomy and the other undergoing assisted reproductive procedures with their partner. After varicocelectomy, mean total testosterone levels increased significantly from 1.77 ± 0.18 ng/mL preoperatively to 3.01 ± 0.43 ng/mL at 12-month follow-up after surgery. In addition, Sathya Srini and Belur Veerachari found that total testosterone levels normalized in 77% of men with hypogonadism, further indicating that varicocelectomy in hypogonadal men could be beneficial. Li et al[56] conducted a systematic review of 9 mostly retrospective studies involving 814 patients undergoing surgical correction for varicocele. They found that mean serum testosterone significantly increased by an average of 97.48 ng/dL after varicocelectomy. Although most data remain retrospective, evidence supporting a potentially beneficial effect of varicocelectomy on serum testosterone levels in hypogonadal men is growing. Thus, hypogonadal men presenting with varicocele could benefit from repair.

CONCLUSIONS

Patient interest in fertility and testicular size preservation and a desire to avoid lifelong medical therapy with testosterone drives the need to identify non-TTh for hypogonadism. Medical therapies that can stimulate endogenous testosterone production include hCG, AIs, and SERMs, all of which demonstrate efficacy in increasing serum testosterone levels and good safety profiles. Natural therapies to increase testosterone production include diet and exercise, weight loss, improved sleep, decreasing stress, and varicocele repair. Diet, exercise, and weight loss provide a means to potentially reverse comorbidities that are closely linked to hypogonadism. Improvements in sleep quality and duration and decreasing stress are additional lifestyle modifications that can improve testosterone levels without the need for lifelong medication. Varicocele repair also can increase testosterone levels, although rigorous data supporting its use remain lacking. Patients considering TTh should be counseled on disease modification and the possibility of discontinuing TTh in the future, before initiation of therapy, and the alternatives discussed in this review also should be considered first in appropriate candidates.

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Conflicts of Interest: Dr Khera is a consultant for AbbVie, Endo, Boston Scientific, Coloplast, and AYTU. Dr Pastuszak is a consultant for Endo and Boston Scientific.

Funding: Dr Pastuszak is a K12 scholar supported by a Male Reproductive Health Research Career Development Physician-Scientist Award (grant HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Program.

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