



Non-testosterone management of male hypogonadism: an examination of the existing literature

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Abstract: Testosterone deficiency is defined as a total testosterone level <300 ng/dL confirmed on two early morning lab draws. Testosterone therapy has historically been offered to men with symptomatic testosterone deficiency in the form of injections, gels, or pellets. However, these treatments are invasive or have undesirable effects including the risk of drug transference. Additionally, testosterone therapy has been associated with increases in hematocrit and controversy remains regarding the risk of cardiovascular and thromboembolic events while on testosterone therapy. As such, much interest has recently been focused on alternative treatment options for testosterone deficiency in the form of orally-administered medications with more favorable side effect profiles. Lifestyle modifications and varicocelectomy have been shown to raise endogenous testosterone production. Similarly, SERMs and aromatase inhibitors (AIs) have been shown to raise testosterone levels safely and effectively. Human chorionic gonadotropin (hCG) remains the only FDA-approved non-testosterone treatment option for testosterone deficiency in men. However, this medication is expensive and requires patient-administered injections. Over the counter herbal supplements and designer steroids remain available though they are poorly studied and are associated with the potential for abuse as well as increased hepatic and cardiovascular risks. This review aims to discuss the existing treatment alternatives to traditional testosterone therapy, including efficacy, safety, and side effects of these options. The authors suggest that the SERM clomiphene citrate (CC) holds the greatest promise as a non-testosterone treatment option for testosterone deficiency.

Keywords: Aromatase inhibitors (AIs); gonadotropins; hypogonadism; selective estrogen receptor modulators (SERMs); testosterone

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Introduction

Hypogonadism, or testosterone deficiency in the male, is defined by the American Urological Association (AUA) as a total testosterone level less than 300 ng/dL on early morning blood draw on two separate occasions (1). Testosterone deficiency is highly prevalent, with rates increasing with age from 4% in men aged 40–49 years to nearly 50% in men over 80 years of age, with some studies

suggesting a 17% increase in testosterone deficiency for every decade of life (2–4).

The AUA Panel on the Evaluation and Management of Testosterone Deficiency suggests that to be eligible for testosterone therapy patients must have low testosterone levels combined with symptoms or signs associated with low testosterone (1). Historically, testosterone deficiency has been treated with various formulations of exogenous testosterone. Exogenous testosterone, however, bypasses

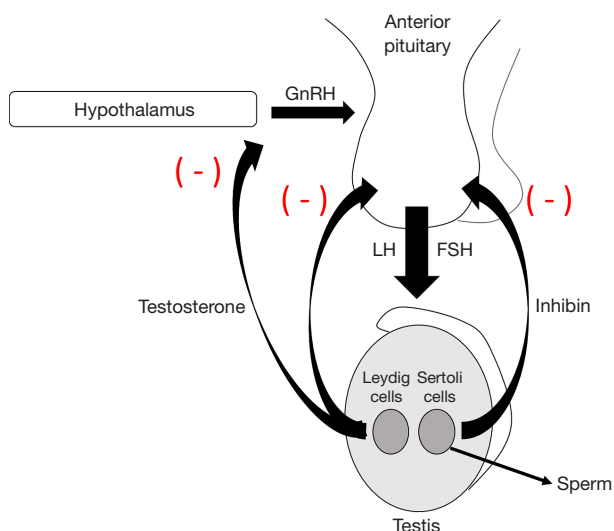


Figure 1 Hypothalamus-pituitary-gonadal axis. The hypothalamus releases GnRH in a pulsatile fashion, which stimulates the anterior pituitary to release LH and FSH to stimulate testosterone production and spermatogenesis in the testis. Testosterone negatively feeds back on the pituitary to suppress LH release. GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.

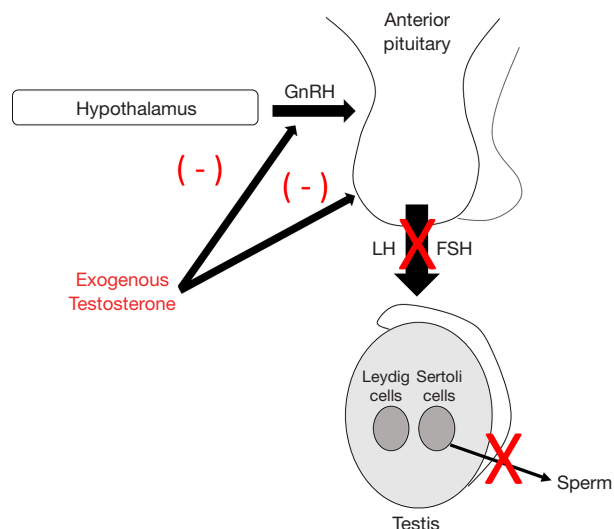


Figure 2 The effect of exogenous testosterone on the HPG axis. Exogenous testosterone suppresses the release of GnRH and LH, resulting in testicular atrophy and suppression of spermatogenesis. HPG, hypothalamic-pituitary-gonadal; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.

the body’s natural ability to produce testosterone, thus leading to the downregulation of luteinizing hormone (LH) and follicle stimulating hormone (FSH) with suppression of the hypothalamic-pituitary-gonadal (HPG) axis and spermatogenesis (5). (Figures 1,2) Additionally, many formulations of exogenous testosterone require invasive administration via injections and can result in large swings in serum testosterone levels with associated recurrence of symptoms. Alternative formulations of exogenous testosterone, such as gels or creams, have the risk of transference to others. Though testosterone therapy improves bone mineral density, lean body mass, erectile function, and anemia, there is inconclusive evidence on the benefits of testosterone therapy on cognitive function, energy levels, blood glucose or lipid levels, and controversy remains around whether testosterone therapy affects the risk of cardiovascular events (6-13). Testosterone therapy may also lead to polycythemia, and while some studies have not linked testosterone therapy to increases in venothrombotic events (VTE), other studies suggest that there is an increased risk of VTE in the first six months of treatment, and warnings regarding cardiovascular and embolic events remain in the drug packaging information (14,15).

Given the side effects and controversies of exogenous testosterone therapy, much work has been done to identify effective alternatives to treat symptomatic testosterone deficiency. This review aims to discuss in detail the options for management of testosterone deficiency in men, outside of exogenous testosterone.

Non-medication management options

Lifestyle modifications

Studies have shown that both low testosterone and obesity increase the risk of major adverse cardiac events (16,17). Recent preliminary data have shown that low endogenous testosterone levels are associated with lower high-density lipoprotein (HDL) cholesterol and higher low-density lipoprotein cholesterol, triglyceride, and total cholesterol levels (18). As such, the AUA recommends counseling men with testosterone deficiency to increase physical activity and maintain their weight within the recommended range to reduce the signs and symptoms of testosterone deficiency and increase serum testosterone levels (1). Armamento-Villareal and colleagues reported that dietary interventions, with and without exercise, resulted in significant increases

in total testosterone levels (19). Similarly, Moran *et al.* reported on 68 men participating in a weight-loss diet. Men lost a mean of 10.3–10.8±1.2 kg over the 52-week study period and experienced significant increases in total and free testosterone ($P<0.001$ and $P=0.002$, respectively). Additionally, men with moderate to severe baseline erectile dysfunction had significant increases in the International Index of Erectile Function (IIEF) erectile function domain following weight loss (20). More recently, Rigon and colleagues evaluated 29 men with a mean baseline weight of 155.26±25.88 kg preoperatively and 6 months postoperatively following bariatric surgery. BMI improved to a mean of 37.82±5.94 kg following surgery, with improvements in total testosterone levels from 229.53±96.45 ng/dL to 388.38±160.91 ng/dL ($P<0.001$) (21).

Aside from maintaining a healthy weight, sleep quality has been associated with symptoms of testosterone deficiency. Pastuszak *et al.* noted a linear relationship between self-reported sleep quality and symptoms of testosterone deficiency as quantified by the Androgen Deficiency in the Aging Male (ADAM) questionnaire (22). Though studies show conflicting results regarding the relationship between sleep hours or quality and testosterone levels, most studies suggest a correlation between sleep quality and symptoms of testosterone deficiency (23). In general, lifestyle modifications to include healthy sleep with diet and exercise to maintain a normal weight and activity level are safe and effectively raise endogenous testosterone levels. These recommendations should be included as part of the counseling and management options for men with testosterone deficiency.

Varicocelectomy

Surgical repair of a varicocele, if present, may also be a treatment option for testosterone deficiency, and has been shown to increase testosterone levels in men with testosterone deficiency. Sathya *et al.* assessed 100 men with primary or secondary infertility, with average testosterone of 177 ng/dL and clinical varicocele, who underwent microscopic varicocelectomy. Following varicocelectomy, testosterone rose significantly to a mean of 301 ng/dL ($P<0.001$) (24). The authors hypothesized that varicocelectomy might improve endogenous testosterone production via reducing testicular hyperthermia, improving the activity of 17,20-desmolase and 17-alpha-hydroxylase enzymes (Figure 3), and improving Leydig cell response to LH stimulation (24). It has been shown that the incidence

of varicocele increases with age and the negative impact of a varicocele on testicular function is progressive, but studies indicate that varicocelectomy improves testosterone levels in hypogonadal men in their 40 and 50s as much as younger men (25–28). Offering varicocelectomy to men with a clinical varicocele and testosterone deficiency may naturally improve endogenous testosterone production and avoid long-term testosterone therapy and associated monitoring and side effects, both in men with subfertility, and in men in whom fertility preservation is not of concern. However, whether those improvements in serum testosterone levels translate into clinically meaningful improvements in symptoms of hypogonadism remains controversial (29). At present, varicocelectomy is not recommended solely for the indication of hypogonadism.

Oral supplements

The discussion of symptoms associated with “low T” in popular culture has led to an increase in demand for products aimed at improving energy levels and sex drive, even among men without a formal diagnosis of testosterone deficiency (30). Many compounds are being marketed as oral dietary supplements or adjuncts to “boost” testosterone. However, studies suggest that oral formulations of testosterone fail to improve symptoms of testosterone deficiency and do not raise serum testosterone levels above placebo due to a lack of bioavailability with an oral formulation (31). Despite this, there is continued interest in oral over-the-counter supplements to treat symptoms of testosterone deficiency (32).

Androgenic-anabolic and designer steroids

Anabolic steroids are compounds synthesized to be structurally like testosterone, but with a longer duration of action and increased bioavailability. These compounds are marketed as performance-enhancing agents. While short-term use may lead to increased muscle mass, long-term use has been associated with increased risks of hepatic dysfunction, carcinoma, and cardiovascular disease, as well as prolonged testicular suppression and subfertility (33–35). “Designer steroids” are androgenic-anabolic steroids chemically modified with the intent to avoid legal restrictions on controlled substances. Many of these compounds are novel, with no published research on their safety or efficacy and have varying anabolic effects, but may still be associated with dependence, hypertension,

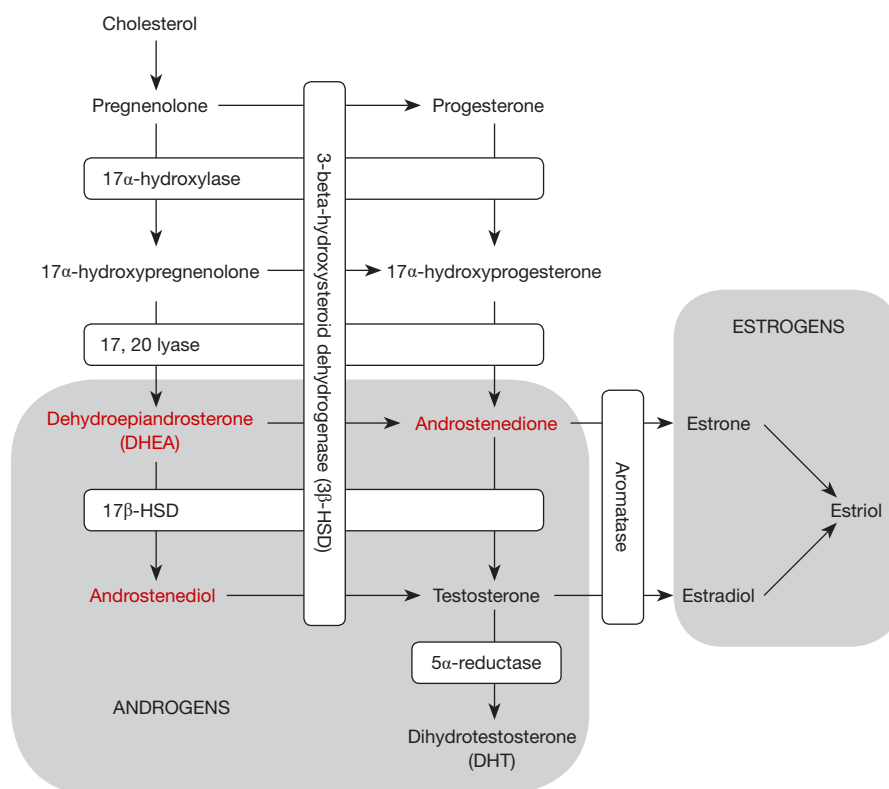


Figure 3 Steroid regulation pathway. Adapted from Kovac JR, Pan M, Arent S, et al. Dietary Adjuncts for Improving Testosterone Levels in Hypogonadal Males. *Am J Mens Health* 2016;10:NP109-17. copyright © 2016 by © SAGE Publications; Reprinted by Permission of SAGE Publications, Inc.

polycythemia, liver toxicity, and subfertility (35).

Kovac and colleagues published a review in 2016 of three commercially available oral testosterone dietary adjuncts marketed to “boost” testosterone, including androstenedione, androstenediol, and dehydroepiandrosterone (DHEA) (30). In 2004, the US Department of Health and Human Services and the Food and Drug Administration passed the Anabolic Steroid Control Act which listed anabolic steroids including androstenedione and androstenediol as controlled substances, making it illegal to obtain these without a physician prescription.

Androstenedione and androstenediol are precursors to testosterone and are converted into testosterone by 17-beta-hydroxysteroid dehydrogenase and 3-beta-hydroxysteroid dehydrogenase, respectively (Figure 3). Studies have shown that oral androstenedione and androstenediol supplementation increases serum levels of androstenedione and estradiol (E2) (36,37). Serum testosterone levels increase but return to the pretreatment baseline after 12 weeks of use (37). The authors hypothesize that this

return to pretreatment baseline testosterone level is due to increased aromatization of peripheral androstenedione and testosterone with conversion to estrone and E2, respectively (37). Neither supplementation with androstenedione or androstenediol improved muscular strength or body composition in patients taking these supplements, and both resulted in worsened HDL cholesterol profiles and increased cardiovascular risk (37).

DHEA is a precursor to androstenedione and androstenediol (Figure 3) and is a weak partial androgen receptor agonist (30). While this compound is regulated in Europe, it is still available over the counter in the United States. A 2013 meta-analysis of 25 randomized controlled trials studying DHEA use in over 1,300 men found that DHEA supplementation was associated with small improvements in body fat composition, but no improvements were noted in total serum testosterone, glucose or lipid profiles, bone mineral density, or mental or physical quality of life outcomes (38). Additionally, studies have shown that DHEA supplementation does not improve

erectile function (39).

Numerous other compounds with steroid-like structures are not regulated and have been identified in dietary supplements marketed to “enhance performance,” with one report finding that synthetic oral anabolic-androgenic steroids have been detected in up to 20% of performance-enhancing drugs sold legally over the counter (35,40,41). This is concerning, as many patients may not be aware of the potential health risks associated with exogenous steroid use, and even if they are, they may not be aware that these compounds are present in their oral supplements. Currently, oral “testosterone boosting” supplements are not recommended for the treatment of testosterone deficiency.

Herbal supplements

Many herbal supplements are also marketed towards “boosting” testosterone levels, including onion (*Allium cepa* L.), ginger (*Zingiber officinale*), maca root (*Lepidium*), fenugreek (*Trigonella foenum-graecum*), Tribulus (*Tribulus Terrestris*), *Tinospora cardifolia*, and black seeds (*Nigella sativa*) (42-44). Onion is thought to work by increasing the production of LH and reducing testicular reactive oxygen species (ROS) (42). Ginger has been hypothesized to improve testosterone production by reducing ROS in the testis (43). *Tribulus Terrestris* and *Tinospora cardifolia* have questionable effects on testosterone levels (30,44). Additionally, most studies have been performed in animals, and data regarding changes in testosterone levels in humans is lacking.

Fenugreek seeds have been touted to have a wide range of health benefits and anti-inflammatory properties and have been used to treat women’s health conditions, diabetes, and hypercholesterolemia (45). It has been suggested that this compound also improves testosterone levels and symptoms associated with testosterone deficiency (46,47). This compound is thought to have androgenic effects via its soluble steroidal saponin content and incomplete 5-alpha reductase and aromatase inhibitor (AIs) activity (47). A study by Maheshwari *et al.* treated 50 men aged 35–65 diagnosed with symptomatic hypogonadism with 500 mg of daily fenugreek seed extract for 12 weeks. Subjects experienced a significant increase in free testosterone (8 *vs.* 12 pg/mL, $P=0.004$), but no significant increase was noted in total testosterone (405 *vs.* 436 ng/dL, $P=0.16$), following 12 weeks of treatment (45). Improvements in sperm count and motility were also noted after 4, 8, and 12 weeks of treatment, with improvements in sperm morphology, noted

at 8 and 12 weeks (45). No changes were noted in DHEA levels, fasting blood sugars, liver enzymes, cholesterol levels, or total leukocyte counts (45). This treatment appears to be well tolerated and effective, but long-term data regarding safety and efficacy are lacking, and further studies need to be performed before the establishment of fenugreek as a viable option for treating testosterone deficiency.

Another compound that has gained interest in the treatment of male hypogonadism is zinc. Zinc deficiency has been linked to decreased spermatogenesis and testosterone production (48). Liu *et al.* randomized 67 men with isolated hypogonadotropic hypogonadism to receive FSH or FSH plus 40 mg zinc for 18 months (48). They found no differences in serum testosterone levels between groups throughout the study period. Similarly, studies suggest that the use of zinc alone is ineffective in increasing testosterone levels (49). Overall, while certain herbal supplements appear to be well tolerated, with preliminary data suggesting increases in testosterone levels, prospective randomized controlled trials in humans must be conducted to demonstrate safety and efficacy before these compounds can be supported for use in the management of testosterone deficiency.

Accepted non-testosterone management options

As exogenous testosterone suppresses spermatogenesis, several compounds are used off-label to treat testosterone deficiency in men desiring to preserve fertility. The AUA states that selective estrogen receptor modulators (SERMs), AIs, and human chorionic gonadotropin (hCG) may be used alone or in combination to treat testosterone deficiency in this population (1). These compounds act at various locations within the HPG axis to upregulate the body’s endogenous testosterone production and serum levels (*Figure 4*).

SERMs

SERMs block the negative feedback of E2 on the hypothalamus, resulting in increased LH production and increased downstream testosterone production (*Figure 4*). These medications are orally administered which improves patient compliance.

The SERM most studied in the treatment of testosterone deficiency is clomiphene citrate (CC). CC has long been used as a treatment to restore testosterone levels and promote or preserve spermatogenesis in men with

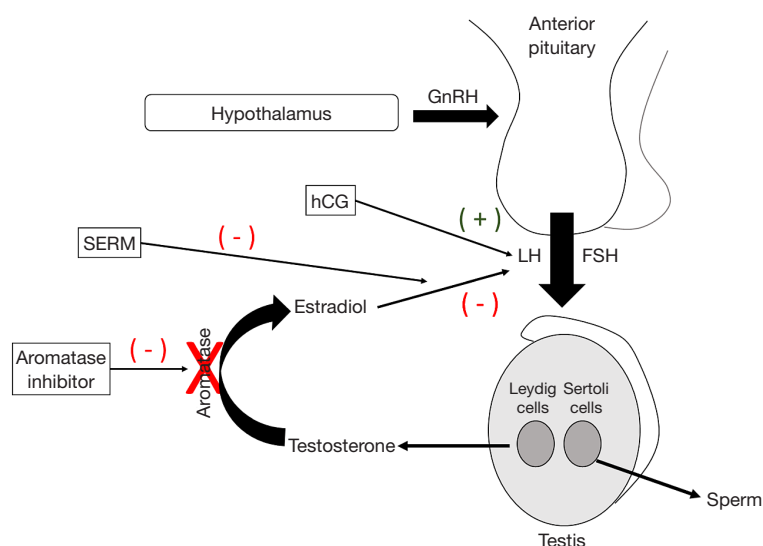


Figure 4 Sites of action of SERMs, aromatase inhibitors, and hCG in the HPG axis. SERMs, selective estrogen receptor modulators; hCG, human chorionic gonadotropin; HPG, hypothalamic-pituitary-gonadal; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.

testosterone deficiency desiring to preserve fertility, and multiple studies have shown that CC effectively raises testosterone to eugonadal levels (50-56). This medication is an oral compound administered at doses ranging from 25 mg every other day, to 50 mg daily, based on testosterone response. Moskovic *et al.* reported on 29 men with a baseline total testosterone level of 228 ± 48 ng/dL treated for >3 years with CC. They demonstrated improvements in testosterone to a mean of 582 ± 227 ng/dL ($P < 0.001$), as well as significant improvements in ADAM questionnaire response ($P = 0.01$) and mean BMI ($P < 0.05$) (50). Similarly, Taylor and Levine demonstrated that compared to testosterone gel therapy, CC treatment resulted in equivalent, significant improvements in testosterone levels at a fraction of the cost, as well as significant improvements in ADAM questionnaire scores. No patients discontinued CC treatment due to side effects, and no adverse events on CC were reported. Additionally, patients on CC treatment did not experience changes in hemoglobin, PSA, or cholesterol levels while on treatment (51). Ramasamy *et al.* have also demonstrated that quantitative ADAM scores were similar among patients treated with CC as compared to those treated with testosterone gels or injections, with improvements in testosterone levels while on CC treatment to physiologic levels (54).

Still, CC has not historically been offered as a first line treatment for testosterone deficiency in men not desiring

fertility preservation given its off-label use and lack of long-term data regarding safety and efficacy. In the setting of these limitations, ongoing studies are being conducted to establish long-term treatment outcomes. CC is well-tolerated. Rare side effects include headaches, visual changes, and gynecomastia (50). Additionally, CC use has shown to have significantly less risk of increased hematocrit as compared to testosterone therapy (57). Preliminary data on men treated for testosterone deficiency on CC for as long as 7 years show that over 80% of men achieve testosterone levels >450 ng/dL, with 78% of men reporting subjective improvement in hypogonadal symptoms, and only 9% reporting side effects from CC treatment with no significant adverse events (58). This data together suggests that CC may be a safe and effective treatment option for the long-term management of testosterone deficiency, and consideration should be made to offering this therapy to men as a first-line treatment option for testosterone deficiency, regardless of the patient's desire for fertility preservation.

Enclomiphene citrate (EC) is a trans-isomer of CC and is not currently FDA approved in the United States. Like CC, EC has been shown to raise testosterone and gonadotropin levels, while preserving spermatogenesis (59). Additionally, EC treatment may deliver the androgenic effects of CC without the side effects associated with CC, though further studies need to be conducted to determine if EC has clinically superior selectivity (60).

Like CC, tamoxifen has been shown to increase testosterone and gonadotropin levels, and preserve spermatogenesis, and this SERM is an acknowledged alternative treatment option for testosterone deficiency in men (1,61). Tamoxifen has been used to stimulate gonadotropin production, and to treat gynecomastia in the setting of anabolic steroid-induced hypogonadism or hCG treatment (62). However, the adverse effects associated with tamoxifen appear to be greater than those associated with CC use, including gastrointestinal distress, venous thromboembolic events, and other cardiovascular outcomes (63). As such, tamoxifen is less commonly used for the treatment of testosterone deficiency.

AIs

Like SERMs, AIs, including letrozole and anastrozole, are also designed to block E2 inhibition of the HPG axis by preventing aromatization of testosterone to E2 in the tissues, thus upregulating endogenous testosterone production (*Figure 4*). These compounds have been shown to raise testosterone levels in hypogonadal men and are also orally administered (64-66). Historically, AIs have been administered concurrently with testosterone therapy to normalize the testosterone-to-estradiol (T:E2) ratio, correct iatrogenic elevations in E2, and treat associated subfertility (67).

Dias *et al.* treated 14 hypogonadal men with 1 mg of anastrozole daily for 12 months. Men treated with AI had significant increases in total testosterone levels over the study course. Of note, lumbar spine bone mineral density was lower in men treated with AI compared to those on testosterone therapy (66). The same group subsequently evaluated the effect of a 12-month treatment of AI on glucose levels and cardiovascular risk markers. After 12 months, fasting glucose, insulin, and lipid levels were not different between men treated with AI and men treated with testosterone therapy (68). However, questions remain regarding the clinical significance of AI-associated changes in testosterone levels and T:E2 ratios, as some studies have failed to show improvements in psychological or physiological parameters or symptoms of hypogonadism with these associated changes (69,70).

AIs are well-tolerated, but side effects may include nausea, the elevation of liver enzymes, headaches, and hot flashes (71). As long-term AI use has been associated with decreases in bone mineral density due to suppression of E2, the AUA recommends against the use of AI for prolonged

periods (1,72). Additionally, if used to correct the T:E2 ratio, a dose of 1 mg two to three times per week is suggested (67).

Gonadotropins

Gonadotropin replacement therapy is an option for treating hypogonadotropic hypogonadism and includes gonadotropin-releasing hormone (GnRH) and the LH analog hCG. Both compounds can be administered subcutaneously. GnRH administration requires the use of a continuous infusion pump to titrate GnRH levels to mimic the pulsatile release of GnRH from the hypothalamus, and this treatment modality is still considered experimental (67).

Of the non-testosterone compounds used to treat testosterone deficiency in men, only hCG is FDA approved (1). hCG is an LH analog and stimulates testosterone production by binding LH receptors. hCG has also been used with concurrent exogenous testosterone to maintain intratesticular testosterone levels and preserve spermatogenesis (73). Liu *et al.* randomized 40 hypogonadal men over the age of 60 to receive either 5,000 IU of hCG or placebo twice per week for 3 months. Patients treated with hCG had significant increases in total and free testosterone (74). More recently, Habous *et al.* treated 94 men with 5000 IU of hCG twice per week for 3 months. They similarly found significant increases in testosterone levels with hCG treatment (75). While hCG acts directly on the testis and is well-tolerated, this medication is expensive, and with the requirement for multiple injections per week, many patients elect alternative treatments (34).

Future directions

Several novel targets for increasing endogenous testosterone production are being investigated. Nerve growth factor has been shown to increase testosterone and LH levels in mice and is thought to promote the pulsatile synthesis and release of GnRH (76). Luo *et al.* recently demonstrated that intranasal delivery of nerve growth factor twice per week for 12 weeks in senescent mice resulted in increased levels of LH, FSH and testosterone, increased intratesticular testosterone, and increases in measures of sexual behavior in mice, including mounting and ejaculation times (76). If these results are reproducible in humans, intranasal nerve growth factors would be a promising minimally-invasive treatment option to promote the restoration of endogenous testosterone production. Similarly, oxytocin has also been shown to stimulate GnRH release, and it has been

hypothesized that intranasal oxytocin may be a potential therapeutic option for testosterone deficiency in the future (77,78). Additionally, research into herbal compounds for the treatment of testosterone deficiency is ongoing (79,80).

Lastly, recent interest has increased around selective androgen receptor modulators (SARMs). SARMs are a newer class of agents with tissue-specific effects like those seen with SERMs and can be tailored to have specific effects within certain tissues while reducing undesired non-specific or androgenic side effects. These compounds are currently being investigated as treatment options for hypogonadism, as they are orally administered and are relatively well-tolerated with few adverse events, though some concern exists as to whether these lead to hepatotoxicity and decreased levels of HDL cholesterol (81).

Conclusions

Given the prevalence of testosterone deficiency in men, and the desire to avoid testosterone therapy and its associated effects on testicular volume, spermatogenesis and the HPG axis with possible adverse side effects, much work has been done to identify safe and efficacious alternative treatment options. Lifestyle modifications are safe and have been shown to increase endogenous testosterone production and should be offered to all men desiring treatment of testosterone deficiency. Varicocelectomy, with further study, may become a valid treatment option in the presence of a clinical varicocele. While numerous compounds exist marketed towards “boosting testosterone,” data on the safety and efficacy of these are poor, and these are not currently recommended as treatments for testosterone deficiency. Gonadotropins, including hCG (the only non-testosterone agent FDA approved for the treatment of male hypogonadism), are effective, but costly and require administration via injection. AIs may also raise testosterone levels but may be associated with decreases in bone mineral density if used long-term. SERMs, including clomiphene citrate, appear to be highly effective at producing physiologic testosterone levels and appear to be well-tolerated and safe when used long-term. Consideration may be given to offering clomiphene citrate to men with symptomatic testosterone, regardless of the patient’s desire to preserve fertility. While studies exist suggesting that many of these treatment options are well tolerated and efficacious, further prospective studies must be conducted to support their use as first line treatment options in the management of testosterone deficiency.

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Footnote

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