Exogenous testosterone replacement therapy versus raising endogenous testosterone: Current and future prospects

Kajal Khodamoradi, M.S., Zahra Khosravizadeh, M.S., Madhu Parmar, B.S., Manish Kuchakulla, B.S., Ranjith Ramasamy, M.D, Himanshu Arora

PII: S2666-5719(20)30009-8

DOI: https://doi.org/10.1016/j.xfnr.2020.11.001

Reference: XFNR 7

To appear in: *F&S Reviews*

Received Date: 22 April 2020

Revised Date: 5 November 2020

Accepted Date: 8 November 2020

Please cite this article as: Khodamoradi K, Khosravizadeh Z, Parmar M, Kuchakulla M, Ramasamy R, Arora H, Exogenous testosterone replacement therapy versus raising endogenous testosterone: Current and future prospects, *F&S Reviews* (2020), doi: https://doi.org/10.1016/j.xfnr.2020.11.001.

Short Running Title- Comparing therapies for low testosterone

Exogenous testosterone replacement therapy versus raising endogenous testosterone: Current and future prospects

Kajal Khodamoradi, M.S.[1]; Zahra Khosravizadeh, M.S.[1]; Madhu Parmar, B.S.[1]; Manish Kuchakulla, B.S.[1]; Ranjith Ramasamy, M.D[1]; Himanshu Arora[1,2#]

[1]Department of Urology, Miller School of Medicine, University of Miami, Miami, FL, USA

Address: 1600 NW 10th Ave #1140, Miami, FL 33136, USA

[2]The Interdisciplinary Stem Cell Institute, University of Miami, Miller School of Medicine, Miami, Florida

Address: 1501 NW 10th Avenue, Suite 909, Miami, FL 33136, USA

Kajal Khodamoradi: kxk687@miami.edu,

Zahra Khosravizadeh: zahra.khosravizadeh@yahoo.com

Madhu Parmar: m.parmar@med.miami.edu

Manish Kuchakulla: m.kuchakulla@med.miami.edu

Ranjith Ramasamy: Ramasamy@miami.edu

[#]Corresponding author

Himanshu Arora, PhD

150A NW 10TH Ave, Suite 832

Miami, FL 33136

Tel: + 1 305 243 4562

Fax: + 1 305-243-6597

Email: hxa287@miami.edu

Support: No grants or fellowships supporting the writing of this paper.

Disclosures: No disclosures

Abstract

Testosterone replacement therapy is an important treatment option for men with low testosterone and symptomatic hypogonadism. Various formulations of exogenous testosterone replacement therapy exist, including oral, buccal, intramuscular, transdermal, subdermal, and nasal preparations. However, exogenous testosterone replacement therapy is a double-edged sword, posing risks to fertility due to negative feedback mechanisms on the hypothalamic-pituitary-gonadal (HPG) axis, which is the main regulator of testosterone production and spermatogenesis in males. Alternative pharmacologic therapies are being used to increase endogenous testosterone levels while attempting to preserve fertility and function of the HPG axis. These include selective estrogen receptor modulators, gonadotropins, and aromatase inhibitors. This review focuses on overviewing and comparing the currently available methods of exogenous testosterone replacement therapy, alternative treatments to increasing endogenous testosterone, and novel treatments that are currently under investigation to normalize testosterone levels while preserving the function of the HPG axis. In conclusion, reports suggest that, though Testosterone replacement therapy is an important way to restore testosterone levels and reduce symptoms associated with low testosterone, it is often difficult to decide which treatment to select for patients with testosterone deficiency. Several factors need to be considered to decide on optimal therapy option for the patient which include but are not limited to safety, efficacy, cost-effectiveness, dosing flexibility, and side effects. Alternative approaches which aim to improve endogenous testosterone production and preserve fertility are promising but still are at their initial stages of development. Ultimately, patient-centered decision making is paramount to appropriate treatment selection.

Key words: low testosterone, testosterone replacement therapy, hypothalamic-pituitary-gonadal axis, male infertility

Essential points:

The manuscript reviews the available methods of exogenous testosterone replacement therapy which are but not limited to oral, buccal, intramuscular, transdermal, subdermal, and nasal, respectively.

The manuscript reviews the alternative therapies to increase endogenous testosterone replacement which includes but not limited to Selective estrogen receptor modulators, gonadotropins, and Aromatase inhibitors, respectively.

Furthermore, the review highlights Investigational therapies to increase endogenous testosterone such as Selective androgen receptor modulators and Leydig stem cell transplantation, respectively.

Moreover, the review compares the core impacts of these therapy options on hormone levels and modulation of HPG axis.

Introduction

Testosterone, a steroid hormone, is the primary androgen in males and is essential for various biologic processes, including reproductive and sexual function, metabolism, body composition, and cognition (1-3). Male hypogonadism, also known as testosterone deficiency (TD), is defined as having one or more symptoms attributable to low circulating levels of testosterone (serum total testosterone <300 ng/dL) (1, 4, 5). Symptoms of TD include decreased libido, erectile dysfunction, decrease in muscle mass and strength, decrease in bone mass, anemia, increase in central body fat, and impaired memory, mood, concentration, and sleep (6, 7).

TD increases with age, with approximately a 1% annual decrease in free testosterone levels after age 30 (6, 7). However, the exact prevalence is unclear due to the varying testosterone level thresholds and non-standardized methodology used in measuring prevalence in population-based studies (5, 8, 9). The pathophysiology of hypogonadism can be characterized into two types: primary (hypergonadotropic hypogonadism) and secondary (hypogonadotropic hypogonadism). Primary hypogonadism is a TD due to a testicular abnormality impairing testosterone production; for example, Klinefelter syndrome, testicular tumors, infection, trauma, impaired Leydig cell function, or those caused by certain medications (2). Secondary hypogonadism is a TD due to a hypothalamic or pituitary abnormality that disrupts stimuli to the testes essential for testosterone production (i.e., luteinizing hormone (LH) and follicle-stimulating hormone (FSH)); for example, hypothalamic or pituitary lesions, GnRH deficiency, or hyperprolactinemia (2). Another important etiology of hypogonadism is late-onset hypogonadism, an age-related (i.e., >40 years) decline in testosterone accompanied by clinical symptoms that is often associated with obesity, diabetes, and other chronic health conditions (7, 10-12).

Several treatments are currently available to reestablish testosterone levels and improve TD symptoms. This review addresses the various forms of exogenous testosterone replacement therapy along with their individual benefits and risks. It also delves into alternative and investigational therapies for TD that aim to mitigate the undesired effects of male infertility and hypothalamic-pituitary-gonadal axis disruption by increasing endogenous testosterone (Table 1).

Available methods of exogenous testosterone replacement therapy

The full spectrum of testosterone action in the body can only be achieved if testosterone is aromatized to estradiol and 5 alpha-reductase to dihydrotestosterone (DHT) (13). Testosterone is generally successful when taken orally and is absorbed well in the intestine, but at times it can be so rapidly metabolized by the liver that it is sometimes ineffective via this route (14). Due to this, a variety of preparations have been developed including oral, buccal, intramuscular, transdermal, subdermal, and nasal preparations. This section includes examples of each preparation and details about their administration, advantages, and disadvantages. These details are summarized in Table 2.

Oral

Currently, the most commonly available oral preparation is testosterone undecanoate. This preparation is able to avoid first passing through the liver due to its aliphatic side chain which allows it to be absorbed by the lymph system and directly enter the circulatory system (13). This formulation requires more frequent and larger doses in order to effectively replete testosterone therapy (15). Resent study reported that although oral testosterone undecanoate is a safe and effective means to treat hypogonadal men, it was related to a small but significant increased

systolic blood pressure (16). While it has shown efficacy, pharmacokinetic analysis has proven that it is difficult to predict absorption due to high intra- and inter-individual variability in serum concentrations. Oral Testosterone undecanoate also includes a black box warning regarding blood pressure increases and risk of cardiac events, which makes its use a major concern for older men. An additional group of oral agents exist that have been available for decades; these are 17-alpha alkylated androgens (methyltestosterone and fluoxymesterone). However, many reports have implicated these oral preparations in cholestatic jaundice, a hepatic cystic disease called peliosis hepatis, and hepatoma (17, 18). Therefore, they are no longer suggested for use due to the discovery of extreme liver toxicity and minimal effectiveness in resolving hypogonadal symptoms.
a black box warning re BP increases

Buccal
Currently, the most commonly available buccal preparation is a buccal tablet (Striant®) which exists as a potential therapeutic option for patients who can tolerate it. The tablets are mucoadhesive and are applied to a depression in the gum above the upper incisors, slowly releasing testosterone into the circulatory system. Twice daily applications of 30 mg tablets result in stable serum levels of testosterone. The benefits of this method are that the effects can quickly be reversed and the release of medication mimics circadian rhythms (14, 19). However, it has also been shown that 3-15% of patients may experience irritation, inflammation, or gingivitis while also having difficulty from complaints due to the unique method of delivery (20). These potential side effects should be taken into consideration when opting for this method of TRT.

Intramuscular
Intramuscular substitution of testosterone has proven to be effective in initiating and maintaining virilization in all hypogonadal men (14). Current options include long-acting (testosterone enanthate and testosterone cypionate) and extra-long-acting (testosterone undecanoate) variants. The long-acting options are esters of testosterone which make the molecule more lipophilic than the natural variant. This results in their storage and gradual release, thereby prolonging the presence of testosterone in the blood (21, 22). Administration of long-acting intramuscular testosterone usually occurs as 50–100 mg every week, 100–200 mg every 2 weeks, or 250 mg every 3 weeks and has shown consistent results (14). The advantages of long-acting options are that they are extremely effective, easily accessible, and cost effective, and they free patients from daily administration. Conversely, the disadvantages are the need for patients to be comfortable with deep intramuscular administration of the solution and fluctuations in energy, mood, and libido in many patients.

An extra-long-acting option exists with testosterone undecanoate in oil, which is also one of the common oral options. When injected alongside castor oil, a half-life of 34 days is observed (13). Each dose is 750 mg in 3mL of oil. The recommendations for administration in the United States are to administer a dose into the buttocks, followed by a second dose 4 weeks later, and then subsequent doses every 10 weeks. Access to this option is regulated by a restricted program called the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program and is not recommended consistently. Although the injectable preparation is generally considered safe, patients must be monitored for pulmonary oil micro-embolism (POME) (23). Symptoms of POME, such as sudden onset of non-productive cough associated with faintness following injections, have been observed in 1.5% of patients (24). Additionally, anaphylactic responses have been observed in some patients, requiring 30-min post-dose monitoring to rule out this side effect (14). The advantages of less frequent administration come at the cost of various systemic side effects that require regular monitoring.

Transdermal

Transdermal preparations are known to provide very stable and effective improvements in serum T levels due to their pharmacokinetic profile which mimics physiological diurnal variations. They include preparations that incorporate solutions, gels, and patches. Three testosterone gels (AndroGel®, Testim®, and Fortesta®), one solution (Axiron®), and one patch (Androderm®) are available in the United States (14). Transdermal testosterone substitution has the following advantages: a) since they have a short duration of action, the preparations can be quickly discontinued if any adverse effect occurs and the testosterone levels will then quickly decline, and b) they are easy to use and easily accessible to many. Conversely, the disadvantages include the need for daily administration, relatively high cost, skin irritation, and the risk of contact transfer to another person (25). The high risk of unintentional transfer led the FDA to require testosterone gel products to include a Blackbox warning. They have also been shown to be less effective in obese individuals and require higher doses (14). However, due to the ease of use, accessibility, and reversibility, these are often a first-line choice for patients who require testosterone substitution.

Subdermal

Subdermal pellet implants (Testopel®) are a viable option for testosterone replacement and result in stable testosterone levels. The pellets are implanted into the subdermal fat of the buttocks, lower abdominal wall, or thigh with a tunneling technique using a local anesthetic (26). It is recommended that three to six 75mg pellets should be implanted every 4-6 months (150 mg-450 mg) to achieve stable testosterone levels in the normal range (14). The benefits of this method include guaranteed compliance and lack of transference to persons who may come in contact with it (14). Adverse effects include pellet extrusion, infection, and fibrosis (27). Due to the need for a surgical procedure for implantation and the sequela of side effects, this form of TRT is usually not recommended as first-line treatment (28).

Nasal

A nasal testosterone gel, known as Natesto®, is now available in the United States for treatment of male hypogonadism. Studies have shown successful treatment with this new method and have exhibited consistent improvements in testosterone deficiency (29). This gel is administered in the nostrils via a metered dose pump which delivers 5.5mg per actuation. The recommended dosage is to administer one actuation in each nostril three times daily, resulting in a daily dosage of 33 mg/day. This method has shown a reduction in gel transfer to a partner or child due to the inconspicuous application site, and it provides ease of use as a non-invasive option. Most importantly, preliminary studies have demonstrated that Natesto® increases serum testosterone while also maintaining FSH, LH, and semen parameters (30, 31). Natesto can maintain spermatogenesis in >95% of men, in contrast to injections or gels (32, 33). Also, significant differences have been observed between duration of action, frequency of administration and clinical pharmacokinetic profile of Natesto compared to long-acting testosterone injections, gels and pellets (34, 35). On the other hand, more than 3% of men have reported experiencing rhinorrhea, epistaxis, nasopharyngitis, sinusitis, and nasal scab as a result of this medication (14). Unique among the formulations of exogenous TRT, nasal formulations of testosterone are showing promise in alleviating symptoms of low testosterone without adversely affecting the hypothalamic-pituitary-gonadal (HPG) axis.

Impact of external testosterone supplementation on the HPG axis

Endogenous testosterone production is stimulated by LH secretion from the pituitary leading to Leydig cell activation. The testosterone produced by LH stimulation participates in a negative feedback axis which regulates pituitary LH synthesis. Thus, when exogenous testosterone is

administered, LH is suppressed from the pituitary resulting in decreased endogenous hormone production and markedly reduced endogenous intratesticular testosterone. The decreased intratesticular testosterone results in low stimulation of spermatogenesis which may cause male infertility (36). Therefore, it is apparent that exogenous testosterone functions as a contraceptive by suppressing LH synthesis and subsequently may lead to markedly reduced sperm counts in nearly all men (37).

A comprehensive medical history, physical examination, and hormonal screening are helpful in determining the potential patients fit to receive TRT (38). TRT is necessary in hypergonadotropic hypogonadism (primary testicular failure), where the serum testosterone level is low and the level of LH is high (38). Although checking serum testosterone levels has increased in men who take TRT, a larger proportion of men might receive treatment without an initial assessment of baseline testosterone concentrations or appropriate monitoring (39).

Patients and health care professionals are not always aware of the potential adverse effect of TRT on normal testicular function (40). In a survey of urologists, 25% reported that they would treat idiopathic infertile males with exogenous testosterone while the patient pursued conception (41). Kolettis et al. (2015) found that 7% of men undergoing infertility evaluation were using supplemental testosterone (42). Furthermore, this study reported the failure of spermatogenesis recovery in more than 20% of these men after TRT cessation, although pre-existing causes of spermatogenesis defect could also be responsible (42). Thus, men considering TRT who desire to preserve their fertility may benefit from a baseline semen analysis (43). A fertility consultation may be beneficial in these patients prior to starting treatment. Furthermore, additional efforts are necessary to establish recommendations for management of infertility in men with hypogonadism, and to raise awareness among physicians about the adverse effects of TRT on spermatogenesis (44).

Alternative therapies to increase endogenous testosterone replacement

Selecting appropriate dosing regimens and formulations of testosterone have been shown to have a lower suppressive capacity on the HPG axis. Additionally, appropriate hormonal monitoring before and during TRT can prevent HPG axis suppression and preserve spermatogenesis (45). However, in addition to these safeguards, there are several alternative therapeutic approaches to raise endogenous testosterone levels other than supplementing exogenous forms of the hormone (44) (Table 3). These include selective estrogen receptor modulators (SERMs), gonadotropins, and aromatase inhibitors that can successfully restore the concentration of testosterone in serum and within the testis as well as preserve fertility (39, 44, 45). Although none of these have been approved by the US Food and Drug Administration (FDA) for the treatment of patients with hypogonadism or infertility, they are commonly used off-label by male fertility specialists. However, a paradoxical decline in the quality of semen and complications related to estrogen level change can be rare unintended effects of these medications (39).

Selective estrogen receptor modulators

SERMs are a group of pharmaceuticals that act as competitive inhibitors of estrogen receptors in the hypothalamus and pituitary with the increasing release of GnRH and gonadotrophins, subsequently increasing production of intra-testicular testosterone and improving spermatogenesis (46). Clomiphene citrate is a SERM that has been used in the treatment of men with azoospermia, oligozoospermia, and unexplained infertility, in addition to treating male hypogonadism. It has been demonstrated that Clomiphene citrate leads to a moderate increase in FSH, LH, total testosterone, and the concentration of sperm in these men (47). Also, in men with late-onset hypogonadism, long-term Clomiphene citrate therapy can be prescribed as a

testosterone replacement (46, 48). Although thromboembolic events and carcinogenesis have been reported as adverse effects of SERMs (49), current ongoing research shows that this group of pharmaceuticals has great potential for future applications (50).

Gonadotropins

Gonadotropin therapy is used to manage infertile patients with low testosterone concentrations, with the aim of recovering normal sperm production. In such patients, stimulating spermatogenesis requires hCG therapy alone or in combination with human menopausal gonadotrophins (hMGs), urinary FSH, or recombinant FSH (46). It has been recommended that TRT with concomitant use of hCG can be prescribed in hypogonadal men who seek fertility treatment (51). Treatment with hCG can preserve normal sperm production in men undergoing TRT by maintaining intratesticular testosterone concentrations (43). Potential side effects of gonadotropin therapy include gynecomastia, headache, fatigue, and mood changes (52). A retrospective study found that treatment of hypogonadal men with TRT and co-administration of low dose hCG maintains semen parameters in these men (53). Coviello et al. (2005) evaluated intratesticular testosterone concentrations from men with normal reproductive physiology who received testosterone enanthate in combination with hCG (125, 250, or 500 IU) (54). A linear increase in intratesticular testosterone concentrations with increased hCG confirms that moderately low dose hCG preserves testicular function in endogenous gonadotropin-suppressed healthy men (54). A systematic review showed that hypogonadal men desiring fertility preservation while benefiting from TRT can be prescribed SERMs or testosterone plus a low dose of hCG. Prescription of hCG alone or in combination with FSH preparations can be recommended to hypogonadotropic hypogonadal patients who need to be treated for infertility (46). In younger men with low serum testosterone levels, treatment with hCG or with Clomiphene citrate will increase serum and intra-testicular testosterone levels without resulting in declining gonadotropin levels via feedback inhibition (55). Overall, hCG is an efficient and safe alternative or adjunct to TRT in men desiring both fertility and treatment for symptoms of hypogonadism. However, a drawback of hCG is that this is an injectable agent.

Aromatase inhibitors

Aromatase inhibitors are a class of drugs that act by blocking aromatase P450 enzymes, consequently normalizing the testosterone/E2 ratio and improving spermatogenesis (56). It has been shown that an aromatase inhibitor (Testolactone) is an effective drug for alleviating infertility in hypogonadotropic hypogonadal obese men (57). However, Testolactone is no longer commercially available. Some men with severe spermatogenic failure who have too much aromatase activity, decreased serum levels of testosterone, increased E2 levels, or impaired testosterone/E2 ratio might benefit from the use of aromatase inhibitors in treating infertility (46). Although no important side effects have been observed with consumption of an aromatase inhibitor for elevating serum testosterone concentrations (46), one study has reported a slight insignificant increase in the level of serum prostate-specific antigen (PSA) in elderly men with low or borderline hypogonadism (58). However, the use of aromatase inhibitors is not suggested due to the absence of long-term data and a limited amount of published literature (45).

Investigational therapies to increase endogenous testosterone

Selective androgen receptor modulators

The pathological effects arising from testosterone has resulted in the search for tissue-selective agonists of the androgen receptor (AR) which could potentially trigger the AR in a tissue-selective manner (59). Selective androgen receptor modulators (SARMs) are a new class of androgen receptor ligands that bind to androgen receptors, depending on the chemical structure of each SARM. Consequently, SARMs lead to anabolic activity while avoiding most of the side effects caused by anabolic steroids (60). The tissue specificity of SARMs has led to the notion

that they may be a promising treatment for a wide variety of diseases (60). SARMs have been studied in the treatment of male hypogonadism and their use is being investigated in clinical trials (6, 60). Miner et al. (2007), in a rat model of sexual behavior, showed that SARMs can lead to increased sexual function. In this model treatment of male rats with 100 mg/kg of a synthetic SARM, LGD226, increased number of mounts, intromissions, and ejaculation (61). Jones et al. demonstrated that administration of S-23 with estradiol benzoate in male rats led to inhibition in spermatogenesis and the suppression of FSH and LH levels. However, these effects are completely reversible (62). Chen et al. reported that C-6, a novel SARM, can mimic *in vivo* endocrine effects of testosterone. Administration of C-6 significantly inhibited spermatogenesis and decreased testosterone concentration, epididymal and testicular size (63). Another study showed that SARM-2f, a novel SARM compound, can restore the sexual behavior in castrated male rats (64). Although SARMs represent an attractive therapeutic approach, further studies are required for the safe use of these medications (60, 65).

Leydig stem cell transplantation

Adult Leydig cells (ALCs), found in the interstitial space of the testis, are the primary source of testosterone production in males (66). ALCs undergo a four-stage process of differentiation, beginning with undifferentiated mesenchymal cells (also known as Leydig stem cells [LSCs]) and progressing to progenitor LCs, immature LCs, and finally to ALCs (67, 68). LSCs do not have steroidogenic capabilities; however, they are unique in that they are capable of replicating indefinitely and differentiating to functioning ALCs (68). This suggests the possibility of having an endless pool of progenitor cells capable of replacing dysfunctional ALCs and restoring testosterone production in men with low testosterone (69). Arora et al. (2018) showed that Leydig stem cells (LSCs) in combination with Sertoli and myoid cells underwent self-renewal as well as differentiation into mature Leydig cells. ALCs act in the HPG axis: an increase in LH stimulates the first step of testosterone synthesis in ALCs; conversely, an increase in testosterone production by ALCs decreases LH production by the pituitary (70). Dysfunction at any point along the HPG axis can lead to testosterone deficiency (71, 72).

Beattie et al. (2015) demonstrated increased testosterone production in rat models by directly stimulating aged ALCs with translocator protein (TSPO), a ligand involved in transporting cholesterol from the cytosol to mitochondria (71). This process was independent of LH regulation and treated aged ALCs had equivalent testosterone production to young ALCs. Other studies have shown great promise in increasing testosterone production at more upstream regulation points. Jiang et al. (2014) showed that transplantation of nestin-positive LSCs into the testis of mice with impaired ALCs caused differentiation into functional ALCs and an increase in testosterone production (73). Zhang et al. (2017) identified that transplanting human p75+ LSCs into EDS-treated rats (inducing ALC dysfunction) successfully replaced the impaired ALCs and partially restored testosterone production (74). Arora et al. (2019) demonstrated a novel form of LSC transplantation by autografting LSCs in combination with Sertoli cells and peritubular myoid cells into the subcutaneous, rather than the testicular, tissue of hypogonadal mouse models (75). This also resulted in differentiation of LSCs into ALCs and increased testosterone production (75).

Conclusion

There has been a dramatic surge in the use of testosterone replacement therapy (TRT) over the past 2 decades (39, 76, 77). With numerous formulations continually being developed, patients and clinicians have many options to choose from with various factors to consider such as efficacy, cost-effectiveness, convenience, safety, and dosing flexibility (78). From 2000 to 2014, an average of 2.6 new transdermal TRT drugs were approved each year (76). Rao et al. (2017)

performed a retrospective cross-sectional analysis assessing trends in TRT use from 2003 to 2013 and found a fourfold increase in TRT use in men ages 18-45, compared with a threefold increase in use in men ages 56-64 (39). However, despite the rise in exogenous TRT, there are concerns about long-term consequences of continued use such as gynecomastia, erythrocytosis, sleep apnea, and the potential risks of heart attack, which cannot be ignored. Therefore, large prospective multiethnic cohort studies are necessary for better clarifying both risk and hazard ratios of TRT (79).

Alternative treatments, including synthetic gonadotropins, selective estrogen receptor modulators (SERMs), and aromatase inhibitors, are being used off-label to raise serum and intratesticular testosterone levels while preserving fertility (39, 80). However, these may have unintended side effects, including decline in semen quality and consequences for bone mineral density and libido due to changes in estrogen levels (80). Thus, there is a need to develop different approaches to restoring testosterone levels in patients that can both reduce negative side effects and preserve the HPG axis and fertility. The future of TRT in men desiring to preserve fertility is moving towards stimulation of endogenous testosterone production by manipulating LSCs. Novel therapeutic approaches of transplanting LSCs in various animal model testis have shown great promise in this endeavor (73, 74). Arora et al. (2019) was the first study of its kind to show successful ALC differentiation, increased testosterone production, and preservation of the HPG axis with subcutaneous autograft of LSCs in hypogonadal mice (75). Further *in vivo* studies are needed to assess efficacy, safety, and clinical applicability of LSC transplant in practice.

References:

1. Carrasquillo R, Chu K, Ramasamy R. Novel Therapy for Male Hypogonadism. Curr Urol Rep 2018;19:63.
2. Seftel A. Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis. Int J Impot Res 2006;18:223-8.
3. Mirone V, Debruyne F, Dohle G, Salonia A, Sofikitis N, Verze P *et al.* European Association of Urology Position Statement on the Role of the Urologist in the Management of Male Hypogonadism and Testosterone Therapy. Eur Urol 2017;72:164-7.
4. Basaria S. Male hypogonadism. Lancet 2014;383:1250-63.
5. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA *et al.* Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol 2018;200:423-32.
6. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Therapeutics and clinical risk management 2009;5:427.
7. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. Am J Med 2011;124:578-87.
8. Anaissie J, DeLay KJ, Wang W, Hatzichristodoulou G, Hellstrom WJ. Testosterone deficiency in adults and corresponding treatment patterns across the globe. Transl Androl Urol 2017;6:183-91.
9. Erenpreiss J, Fodina V, Pozarska R, Zubkova K, Dudorova A, Pozarskis A. Prevalence of testosterone deficiency among aging men with and without morbidities. Aging Male 2019:1-5.
10. Huhtaniemi I. Late-onset hypogonadism: current concepts and controversies of pathogenesis, diagnosis and treatment. Asian J Androl 2014;16:192-202.
11. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD *et al.* Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123-35.
12. Naifar M, Rekik N, Messedi M, Chaabouni K, Lahiani A, Turki M *et al.* Male hypogonadism and metabolic syndrome. Andrologia 2015;47:579-86.

13. Nieschlag E. Current topics in testosterone replacement of hypogonadal men. Best Pract Res Clin Endocrinol Metab 2015;29:77-90.
14. Tsametis CP, Isidori AM. Testosterone replacement therapy: For whom, when and how? Metabolism 2018;86:69-78.
15. Nieschlag E, Mauss J, Coert A, Kicovic P. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. Acta Endocrinol (Copenh) 1975;79:366-74.
16. Swerdloff RS, Wang C, White WB, Kaminetsky J, Gittelman MC, Longstreth JA *et al.* A New Oral Testosterone Undecanoate Formulation Restores Testosterone to Normal Concentrations in Hypogonadal Men. The Journal of Clinical Endocrinology & Metabolism 2020;105:dgaa238.
17. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. Lancet 1977;2:262-3.
18. Henderson JT, Richmond J, Sumerling MD. Androgenic-anabolic steroid therapy and hepatocellular carcinoma. Lancet 1973;1:934.
19. Korbonits M, Kipnes M, Grossman AB. Striant SR: a novel, effective and convenient testosterone therapy for male hypogonadism. Int J Clin Pract 2004;58:1073-80.
20. Dinsmore WW, Wyllie MG. The long-term efficacy and safety of a testosterone mucoadhesive buccal tablet in testosterone-deficient men. BJU Int 2012;110:162-9.
21. Behre HM, Abshagen K, Oettel M, Hubler D, Nieschlag E. Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. Eur J Endocrinol 1999;140:414-9.
22. Fujioka M, Shinohara Y, Baba S, Irie M, Inoue K. Pharmacokinetic properties of testosterone propionate in normal men. J Clin Endocrinol Metab 1986;63:1361-4.
23. Middleton T, Turner L, Fennell C, Savkovic S, Jayadev V, Conway AJ *et al.* Complications of injectable testosterone undecanoate in routine clinical practice. Eur J Endocrinol 2015;172:511-7.
24. Mackey MA, Conway AJ, Handelsman DJ. Tolerability of intramuscular injections of testosterone ester in oil vehicle. Hum Reprod 1995;10:862-5.
25. de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. Hum Reprod 2009;24:425-8.
26. Seftel A. Testosterone replacement therapy for male hypogonadism: part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. Int J Impot Res 2007;19:2-24.
27. Kelleher S, Turner L, Howe C, Conway AJ, Handelsman DJ. Extrusion of testosterone pellets: a randomized controlled clinical study. Clin Endocrinol (Oxf) 1999;51:469-71.
28. Fennell C, Sartorius G, Ly LP, Turner L, Liu PY, Conway AJ *et al.* Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. Clin Endocrinol (Oxf) 2010;73:102-9.
29. Gronski MA, Grober ED, Gottesman IS, Ormsby RW, Bryson N. Efficacy of Nasal Testosterone Gel (Natesto((R))) Stratified by Baseline Endogenous Testosterone Levels. J Endocr Soc 2019;3:1652-62.
30. Masterson T, Molina M, Ibrahim E, Ramasamy R. Natesto Effects on Reproductive Hormones and Semen Parameters: Results from an Ongoing Single-center, Investigator-initiated Phase IV Clinical Trial. Eur Urol Focus 2018;4:333-5.
31. Ramasamy R, Masterson TA, Best JC, Bitran J, Ibrahim E, Molina M *et al.* Effect of Natesto on Reproductive Hormones, Semen Parameters and Hypogonadal Symptoms: A Single-Center, Open-Label, Single-Arm Trial. The Journal of Urology 2020:10.1097/JU.0000000000001078.

32. Kim ED, McCullough A, Kaminetsky J. Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. Bju International 2016;117:677-85.
33. MALE MFTRO. Contraceptive efficacy of testosterone-induced azoospermia in normal men. The Lancet 1990;336:955-9.
34. Rogol A, Tkachenko N, Bryson N. Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology 2016;4:46-54.
35. Rogol AD, Tkachenko N, Badorrek P, Hohlfeld JM, Bryson N. Phase 1 pharmacokinetics and phase 3 efficacy of testosterone nasal gel in subjects with seasonal allergies. Canadian Urological Association Journal 2018;12:E349.
36. Page ST, Kalhorn TF, Bremner WJ, Anawalt BD, Matsumoto AM, Amory JK. Intratesticular androgens and spermatogenesis during severe gonadotropin suppression induced by male hormonal contraceptive treatment. J Androl 2007;28:734-41.
37. Amory JK, Page ST, Bremner WJ. Drug insight: Recent advances in male hormonal contraception. Nat Clin Pract Endocrinol Metab 2006;2:32-41.
38. Hellstrom WJ, Paduch D, Donatucci CF. Importance of hypogonadism and testosterone replacement therapy in current urologic practice: a review. International urology and nephrology 2012;44:61-70.
39. Rao PK, Boulet SL, Mehta A, Hotaling J, Eisenberg ML, Honig SC *et al.* Trends in Testosterone Replacement Therapy Use from 2003 to 2013 among Reproductive-Age Men in the United States. J Urol 2017;197:1121-6.
40. Samplaski MK, Loai Y, Wong K, Lo KC, Grober ED, Jarvi KA. Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters. Fertility and sterility 2014;101:64-9.
41. Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. The Journal of urology 2012;187:973-8.
42. Kolettis PN, Purcell ML, Parker W, Poston T, Nangia AK. Medical testosterone: an iatrogenic cause of male infertility and a growing problem. Urology 2015;85:1068-73.
43. Lee JA, Ramasamy R. Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men. Translational andrology and urology 2018;7:S348.
44. Majzoub A, Sabanegh Jr E. Testosterone replacement in the infertile man. Translational andrology and urology 2016;5:859.
45. Crosnoe LE, Grober E, Ohl D, Kim ED. Exogenous testosterone: a preventable cause of male infertility. Transl Androl Urol 2013;2:106-13.
46. El Meliegy A, Motawi A, El Salam MAA. Systematic review of hormone replacement therapy in the infertile man. Arab journal of urology 2018;16:140-7.
47. Chehab M, Madala A, Trussell J. On-label and off-label drugs used in the treatment of male infertility. Fertility and sterility 2015;103:595-604.
48. Moein MR, Tabibnejad N, Ghasemzadeh J. Beneficial effect of tamoxifen on sperm recovery in infertile men with nonobstructive azoospermia. Andrologia 2012;44:194-8.
49. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clinical interventions in aging 2014;9:1437.
50. Pickar JH, MacNeil T, Ohleth K. SERMs: progress and future perspectives. Maturitas 2010;67:129-38.
51. Dohle G, Arver S, Bettocchi C, Jones T, Kliesch S, Punab M. EAU guidelines on male hypogonadism. European Association of Urology, Arnhem, The Netherlands, accessed Mar 2016;21:2018.
52. Crosnoe-Shipley LE, Elkelany OO, Rahnema CD, Kim ED. Treatment of hypogonadotropic male hypogonadism: Case-based scenarios. World J Nephrol 2015;4:245-53.

53. Hsieh T-C, Pastuszak AW, Hwang K, Lipshultz LI. Concomitant intramuscular human chorionic gonadotropin preserves spermatogenesis in men undergoing testosterone replacement therapy. The Journal of urology 2013;189:647-50.
54. Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD *et al.* Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. The Journal of Clinical Endocrinology & Metabolism 2005;90:2595-602.
55. Pasqualotto FF, Lucon AM, Sobreiro BP, Pasqualotto EB, Arap S. Effects of medical therapy, alcohol, smoking, and endocrine disruptors on male infertility. Revista do Hospital das Clínicas 2004;59:375-82.
56. Ribeiro MA, Gameiro L, Scarano WR, Briton-Jones C, Kapoor A, Rosa MB *et al.* Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: a systematic review of randomized controlled trials. JBRA Assist Reprod 2016;20:82-8.
57. Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. Metabolism 2003;52:1126-8.
58. Leder BZ, Rohrer JL, Rubin SD, Gallo J, Longcope C. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. The Journal of Clinical Endocrinology & Metabolism 2004;89:1174-80.
59. Narayanan R, Coss CC, Dalton JT. Development of selective androgen receptor modulators (SARMs). Molecular and cellular endocrinology 2018;465:134-42.
60. Solomon ZJ, Mirabal JR, Mazur DJ, Kohn TP, Lipshultz LI, Pastuszak AW. Selective androgen receptor modulators: current knowledge and clinical applications. Sexual medicine reviews 2018.
61. Miner JN, Chang W, Chapman MS, Finn PD, Hong MH, López FJ *et al.* An orally active selective androgen receptor modulator is efficacious on bone, muscle, and sex function with reduced impact on prostate. Endocrinology 2007;148:363-73.
62. Jones A, Chen J, Hwang DJ, Miller DD, Dalton JT. Preclinical characterization of a (S)-N-(4-cyano-3-trifluoromethyl-phenyl)-3-(3-fluoro, 4-chlorophenoxy)-2-hydroxy-2-methyl-propanamide: a selective androgen receptor modulator for hormonal male contraception. Endocrinology 2009;150:385-95.
63. Chen J, Hwang DJ, Bohl CE, Miller DD, Dalton JT. A selective androgen receptor modulator for hormonal male contraception. Journal of Pharmacology and Experimental Therapeutics 2005;312:546-53.
64. Morimoto M, Amano Y, Oka M, Harada A, Fujita H, Hikichi Y *et al.* Amelioration of sexual behavior and motor activity deficits in a castrated rodent model with a selective androgen receptor modulator SARM-2f. PloS one 2017;12:e0189480.
65. Bhasin S, Jasuja R. Selective androgen receptor modulators (SARMs) as function promoting therapies. Current opinion in clinical nutrition and metabolic care 2009;12:232.
66. Zhou R, Wu J, Liu B, Jiang Y, Chen W, Li J *et al.* The roles and mechanisms of Leydig cells and myoid cells in regulating spermatogenesis. Cell Mol Life Sci 2019;76:2681-95.
67. Mendis-Handagama SM, Ariyaratne HB. Differentiation of the adult Leydig cell population in the postnatal testis. Biol Reprod 2001;65:660-71.
68. Chen H, Ge RS, Zirkin BR. Leydig cells: From stem cells to aging. Mol Cell Endocrinol 2009;306:9-16.
69. Chen H, Stanley E, Jin S, Zirkin BR. Stem Leydig cells: from fetal to aged animals. Birth Defects Res C Embryo Today 2010;90:272-83.
70. Neaves WB. Leydig cells. Contraception 1975;11:571-606.
71. Beattie MC, Adekola L, Papadopoulos V, Chen H, Zirkin BR. Leydig cell aging and hypogonadism. Exp Gerontol 2015;68:87-91.

72. Winters SJ, Moore JP, Jr., Clark BJ. Leydig cell insufficiency in hypospermatogenesis: a paracrine effect of activin-inhibin signaling? Andrology 2018;6:262-71.
73. Jiang MH, Cai B, Tuo Y, Wang J, Zang ZJ, Tu X *et al.* Characterization of Nestin-positive stem Leydig cells as a potential source for the treatment of testicular Leydig cell dysfunction. Cell Res 2014;24:1466-85.
74. Zhang M, Wang J, Deng C, Jiang MH, Feng X, Xia K *et al.* Transplanted human p75-positive stem Leydig cells replace disrupted Leydig cells for testosterone production. Cell Death Dis 2017;8:e3123.
75. Arora H, Zuttion M, Nahar B, Lamb D, Hare JM, Ramasamy R. Subcutaneous Leydig Stem Cell Autograft: A Promising Strategy to Increase Serum Testosterone. Stem Cells Transl Med 2019;8:58-65.
76. Walter JR, Xu S. Therapeutic transdermal drug innovation from 2000 to 2014: current status and outlook. Drug Discov Today 2015;20:1293-9.
77. Garnick MB. Testosterone replacement therapy faces FDA scrutiny. JAMA 2015;313:563-4.
78. Nieschlag E, Behre HM, Bouchard P, Corrales JJ, Jones TH, Stalla GK *et al.* Testosterone replacement therapy: current trends and future directions. Hum Reprod Update 2004;10:409-19.
79. Grech A, Breck J, Heidelbaugh J. Adverse effects of testosterone replacement therapy: an update on the evidence and controversy. Ther Adv Drug Saf 2014;5:190-200.
80. Thirumalai A, Berkseth KE, Amory JK. Treatment of Hypogonadism: Current and Future Therapies. F1000Res 2017;6:68.
81. Dobs AS, Matsumoto A, Wang C, Kipnes M. Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. Current medical research and opinion 2004;20:729-38.
82. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ *et al.* Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. The Journal of Clinical Endocrinology & Metabolism 2004;89:2085-98.
83. Mazer N, Bell D, Wu J, Fischer J, Cosgrove M, Eilers B. ENDOCRINOLOGY: Comparison of the Steady-State Pharmacokinetics, Metabolism, and Variability of a Transdermal Testosterone Patch Versus a Transdermal Testosterone Gel in Hypogonadal Men. The journal of sexual medicine 2005;2:213-26.
84. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R *et al.* AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. The Journal of Clinical Endocrinology & Metabolism 2003;88:2673-81.
85. Grober E, Khera M, Soni S, Espinoza M, Lipshultz L. Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. International journal of impotence research 2008;20:213-7.

Therapy	Mechanism of Action	Types	Strengths	Limitations
Exogenous Testosterone Replacement Therapy	- Restore testosterone levels by supplementing various preparations of natural testosterone	- Oral, buccal, intramuscular, transdermal, subdermal, and nasal preparations	- Multiple routes of administration depending on patient preference and needs - Improves low testosterone levels and maintains virilization in hypogonadal men - Particularly useful for treating hypergonadotropic hypogonadism in which testosterone levels are low but LH levels are high	- Because it mimics functions of endogenous testosterone, it also exerts negative feedback on the hypothalamus and pituitary gland, reducing LH and decreasing endogenous intratesticular testosterone production - Decreases intratesticular testosterone, impairs spermatogenesis, and results in male infertility
Therapies that Increase Endogenous Testosterone	- Multiple mechanisms of action by affecting various points along the HPG axis to increase endogenous testosterone production	- Selective estrogen receptor modulators (SERMs), Gonadotropins, Aromatase inhibitors, Selective androgen receptor modulators (SARMs), Leydig stem cell transplantation	- Able to increase serum and intratesticular testosterone levels - Greater likelihood of preserving HPG axis function and, subsequently, spermatogenesis and fertility	- Potential unintended decline in quality of semen and complications related to changes in estrogen levels - None have been approved by the US FDA specifically for men with hypogonadism or infertility

Table 1. Exogenous testosterone replacement therapy vs. therapies that increase endogenous testosterone

Names	Strengths	Limitations	Comparative Efficacy	References
Testosterone undecanoate	- Bypasses first-pass liver metabolism due to aliphatic side chain and is absorbed directly by the lymphatic system and then by blood	- Requires large and frequent dosing to mimic physiologic testosterone levels - Serum concentration difficult to predict due to high intra- and inter-individual variability - Risk of increased blood pressure and cardiac events	A small but significant increase in systolic BP versus topical testosterone (gel or patch), A greater number of gastrointestinal-associated side effects compared to topical testosterone. (17)	Nieschlag 2015 (19), Nieschlag et al. 1975 (21), Swerdloff et al. 2020 (16)
Striant®	- Requires only 2x/day dosing to result in stable serum testosterone concentrations and mimics physiologic circadian rhythm release - Medication effects can easily be reversed due to easy access of tablets in the oral cavity	- Side effects of local irritation, inflammation, or gingivitis in some patients	Superior to Androderm (74) Equal to AndroGel (81)	Tsametis & Isidori 2018 (20), Korbonits et al. 2004 (24), Dinsmore & Wyllie 2012 (25)
Long acting: Testosterone enanthate, Testosterone cypionate Extra-long acting: Testosterone undecanoate	- More lipophilic than other formulations allowing for extended storage, gradual release, and prolonged presence of testosterone in the blood - Requires fewer administrations – 2-4x/month (long acting) or 1-2x/2 months (extra-long acting) - Easy access - Cost effective	- Pain associated with deep intramuscular administration - Fluctuations in energy, mood, and libido in many patients - Risk of pulmonary oil microembolism and anaphylaxis with extra-long acting formulation	Equal to AndroGel (82)	Nieschlag 2015 (19), Tsametis & Isidori 2018 (20), Behre et al. 1999 (26), Fujioka et al. 1986 (27), Middleton et al. 2015 (28), Mackey et al. 1995 (29)
Gel: AndroGel®, Testim®, and Fortesta® Solution: Axiron® Patch: Androderm®	- Mimics physiologic diurnal release - Short duration of action, allowing for quick discontinuation - User friendly	- Requires daily administration - High cost - Side effects of skin irritation and potential contact transfer to another person - Less effective in obese individuals	AndroGel equal to Androderm (83) AndroGel equal to Depo Testosterone (82) AndroGel equal to Deletestryl (82) AndroGel Equal to Striant (81)	Tsametis & Isidori 2018 (20), de Ronde 2009 (30),

			Testim superior to Androderm (84) Testim superior to AndroGel (85)	
Testopel®	- Only requires implantation of pellets every 4-6 months - No risk of contact transference	- Necessity for surgical procedure to implant sub dermally - Risk of pellet extrusion, infection, and fibrosis		Tsametis & Isidori 2018 (20), Seftel 2007 (31), Kelleher et al. 1999 (32), Fennell et al. 2010 (33)
Natesto®	- Decreased risk of transference due to inconspicuous site of application - Non-invasive and user-friendly - Increases testosterone, while maintaining FSH, LH, and semen parameters	- Side effects of rhinorrhea, epistaxis, nasopharyngitis, sinusitis, and nasal scabbing	Maintenance of spermatogenesis in >95% of men, in contrast to injections or gels, Short duration of action, frequency of administration and clinical pharmacokinetic profile compared to long-acting testosterone injections, gels and pellets.(32)	Tsametis & Isidori 2018 (20), Gronski et al. 2019 (34), Masterson et al. 2018 (35), Kim et al. 2016 (32), MALE et al. 1990 (33), Rogol et al. 2016 (34), Rogol et al. 2018 (35)

Table 2. Formulations of exogenous testosterone replacement therapy

Class	Mechanism of Action	Strengths	Limitations	References
Selective Estrogen Receptor Modulators (SERMs)	- Mixed estrogen agonist/antagonist properties in different tissues - In the pituitary gland, acts as an antagonist, thus stimulating the release of LH and FSH, which drive both testosterone production and spermatogenesis	- Successful in treatment of azoospermia, oligospermia, male hypogonadism, and unexplained male infertility	- Increased risk of thromboembolic events and carcinogenesis	El Meliegy et al. 2018 (56), Chehab et al. 2015 (57), Moein et al. 2012 (58), Martinkovich et al. 2014 (59), Pickar et al. 2010 (60)
Gonadotropins	- Mimics effects of endogenous gonadotropins and is particularly useful in the treatment of hypogonadotropic hypogonadism - Like endogenous gonadotropins, stimulates testosterone production and spermatogenesis	- Successful in treatment of hypogonadal men, while maintaining semen parameters, intratesticular testosterone, and fertility - Useful for preserving spermatogenesis in men undergoing exogenous TRT by maintaining intratesticular testosterone levels	- Side effects of gynecomastia, headache, fatigue, and mood changes	Pasqualotto et al. 2004 (38), Lee & Ramasamy 2018 (44), El Meliegy et al. 2018 (56), Dohle et al. 2016 (61), Crosnoe-Shipley et al. 2015 (62), Hsieh et al. 2013 (63), Coviello et al. 2005 (64)
Aromatase Inhibitors	- Blocks aromatase conversion of testosterone to estradiol, thereby increasing testosterone levels and normalizing the testosterone/estradiol ratio	- Useful in treating infertility in obese men with hypogonadotropic hypogonadism	- Potential increase in PSA level in elderly men with low or borderline hypogonadism - Limited long-term data to assess efficacy and adverse effects	Crosnoe et al. 2013 (55), El Meliegy et al. 2018 (56), Ribeiro et al. 2016 (65), Zumoff et al. 2003 (66), Leder et al. 2004 (67)
Selective Androgen Receptor Modulators (SARMs)	- Selective agonist of tissue-specific androgen receptors, mimicking the effect of testosterone in certain tissues	- Potential use in the treatment of male hypogonadism and infertility	- Currently in investigational phase; further studies are required to assess safety and efficacy	Bassil et al. 2009 (6), Narayanan et al. 2018 (68), Solomon et al. 2018 (69), Miner et al. 2007 (70), Bhasin & Jasuja 2009 (71)
Leydig Stem Cell Transplantation	- Leydig stem cells can differentiate into adult Leydig cells, which produce intratesticular testosterone under stimulation of LH	- Successful studies showing increased testosterone production in various animal models	- Further studies are required to prove effectiveness and safety in humans	Zang et al. 2017 (72), Beattie et al. 2015 (75), Mendis-Handagama & Ariyaratne 2001 (77), Chen et al. 2009 (78), Chen et al. 2010 (79), Jiang et al. 2014 (80), Zhang et al. 2017 (81), Arora et al. 2019 (82)

Table 3. Therapies that increase endogenous testosterone