Expert Opinion

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Current and future testosterone delivery systems for treatment of the hypogonadal male

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Background: Hypogonadism is manifest in all age groups, and a growing elderly population is requiring treatment for testosterone deficiency, presenting new safety challenges, as many of these individuals present with comorbidities and significant risk profiles. *Objective*: To discuss testosterone replacement modalities, their advantages and disadvantages, and provide a discussion of safety issues. *Methods*: We reviewed the literature regarding testosterone replacement therapy and have provided a summary of our most outstanding findings. *Conclusion*: Potential benefits of testosterone replacement therapy include increased lean body mass, heightened libido, increased bone density and elevation of mood. Some disadvantages are clearly defined, while others require further investigation. Patient and physician must cooperate to agree on an individual patient's most appropriate and tolerable route of administration.

Keywords: age-dependent testosterone declines, hypogonadism, safety, testosterone deficiency, testosterone replacement therapy

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1. Introduction

1.1 Male hypogonadism

Affecting approximately 4 – 5 million in the US alone, and a speculated 481,000 new cases being diagnosed yearly in the 40 – 69 age group [1], male hypogonadism comprises a major treatment issue in the current patient population. It is defined as a failure of the testes to produce adequate amounts of testosterone or perform spermatogenesis. Male hypogonadism may be primary (affecting the testes) or secondary (affecting the pituitary or hypothalamus). Deficiency of testosterone *in utero* can result in ambiguous genitalia. The onset of hypogonadism prior to puberty leads to development of a eunuchoid body habitus, lack of secondary sexual characteristics and delayed puberty. In adults, abnormally low levels of testosterone can result in a variety of nonspecific effects, including decreases in bone mass, libido, lean body mass, spermatogenesis and general well-being.

Gonadotropin releasing hormone (GnRH) from the hypothalamus acts on the adenohypophysis of the pituitary gland to synthesize and secrete luteinizing hormone (LH) and follicule stimulating hormone (FSH) into the bloodstream. LH acts on the Leydig cells of the testes to release testosterone. A portion of the testosterone released is bound in the blood by sex hormone binding globulin (SHBG), while the unbound testosterone is available to bind the androgen receptor. Primary hypogonadism (hypergonadotropic hypogonadism, characterized by an elevated LH and FSH) can result from genetic defects such as Klinefelter's syndrome or direct trauma to the testes (injury, chemicals, radiation). Secondary hypogonadism (hypogonadotropic hypogonadism with relatively low levels of

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LH and FSH) can be due to disease or injury of the hypothalamus or pituitary.

A concept deserving of attention is that of a decline in testosterone levels related to age. The Baltimore Longitudinal Study on Aging, which followed the serum total and free testosterone levels in 890 men, found that approximately 20% of the men in their study over the age of 60 had testosterone levels in the hypogonadal range, with the proportion of individuals in this range increasing with age [2]. Age-dependent declines in circulating testosterone are due to a combination of both secondary (pituitary insufficiency) and primary (testicular failure) mechanisms and are likely to be the result of age and co-morbidities. Symptoms that may be encountered in hypogonadal men include, but are not limited to, breast discomfort, a reduced need for shaving, decreased size of testes, decreased libido, reduced lean body mass, low bone mineral density and depression [3-5]. It is important for the practitioner to recognize these signs in his or her patient and test serum testosterone levels.

2. Testing for hypogonadism

Male hypogonadism is diagnosed by the documentation of decreased serum testosterone levels, typically under the threshold of 11 nmol/l for total testosterone and 0.225 nmol/l for free testosterone in adult men, as well as clinical symptoms [6]. Although this appears straightforward, it assuredly is not. These are the standards for young men, and although they are also used as standards in the aging population, it is not yet clear as to whether this is entirely appropriate. In addition, serum testosterone levels have a diurnal variation, with peak levels in the morning hours. Typically samples need to be drawn between 8:00 and 10:00 am in a fasting state to circumvent this variation [6]. The current gold standard for measurement of total testosterone is by liquid chromatography-tandem mass spectrometry. A measure of free serum testosterone should be performed in men with borderline levels of total testosterone. Options include free testosterone via the equilibrium dialysis or ammonium sulfate precipitation method, assays for bioavailable testosterone, or measurement of total testosterone with SHBG for calculation of a free androgen index.

Even accounting for changes in level according to the time of day, there is still considerable variation among testing centers in what is considered a normal range. In a study looking at 12 academic laboratories, 12 community laboratories and one national laboratory, out of the 25 labs there were 17 and 13 different reference ranges for total and free testosterone, respectively [7]. In addition, only four and seven labs had age-adjusted values for total and free testosterone, respectively, and 23 out of the 25 lab directors stated a preference for clinically relevant reference ranges over their current statistically based model [7]. As such, one can see the importance of including clinical symptoms in the diagnostic criteria for hypogonadism.

3. Testosterone replacement

In 1889 Charles Edward Brown-Sequard, whom some consider to be one of the founders of modern endocrinology, injected himself with an aqueous extract of crushed guinea pig and canine testicles. After doing this he reportedly stated that 'the injections have taken 30 years off my life,' and described improvement in his intellect, sexual potency and urinary stream. Years later, in 1920, a man by the name of Serge Voronoff completed the first official testicular tissue transplant from a chimpanzee to a human with the goal of rejuvenation in old age, and reportedly went on to complete 2,000 of these transplants in his lifetime [8]. Although of interest, the purported effects of these treatments more than likely represent the power of the placebo effect.

Modern testosterone replacement reaches back as far as the 1940s with the introduction of subdermal testosterone implants [9]. Since then a number of other modalities have become available to prescribers (see **Figure 1**). The developers of these preparations face the challenges of providing ease of administration, reasonable prices, and adequate duration of action and mimicking fluctuations in the serum hormone levels. It has proven difficult to reproduce the normal physiologically diurnal fluctuations of testosterone in the healthy male via replacement therapy. However, a number of preparations have been demonstrated to reverse or prevent some of the signs and symptoms of hypogonadism (see **Table 1**). These will be discussed below, along with the advantages and disadvantages of each preparation.

3.1 Topical applications

3.1.1 The patch system

The transdermal scrotal patch became available in 1994, shortly after which nonscrotal patches were introduced. The scrotal patch (Testoderm®) must be applied to a hair-free area of the scrotum and worn for 24 h. Testosterone levels are reported to reach a peak at 2 – 4 h and are held in the normal range for the full 24 h the patch is worn. A new patch must be applied immediately after the previous patch is removed, as testosterone levels decline rapidly. Patients generally report an improvement in energy, mood and sexual functioning. However, the scrotal patch is no longer sold in the US because it may cause scrotal irritation, is inconvenient for many patients and cannot be used in cases where the scrotal area is too small. Other more suitable options have replaced it, including the nonscrotal testosterone patches.

Nonscrotal testosterone patches (Androderm® and Andropatch®) are applied at night and are available in 5-mg and 2.5-mg preparations that can be used in conjunction to individualize treatment. One trial demonstrated that, in patients previously treated with intramuscular preparations who had undergone a washout period, the percentage of time patient testosterone levels were in the normal range was 72.0% when re-started on intramuscular treatment. The percentage of time was

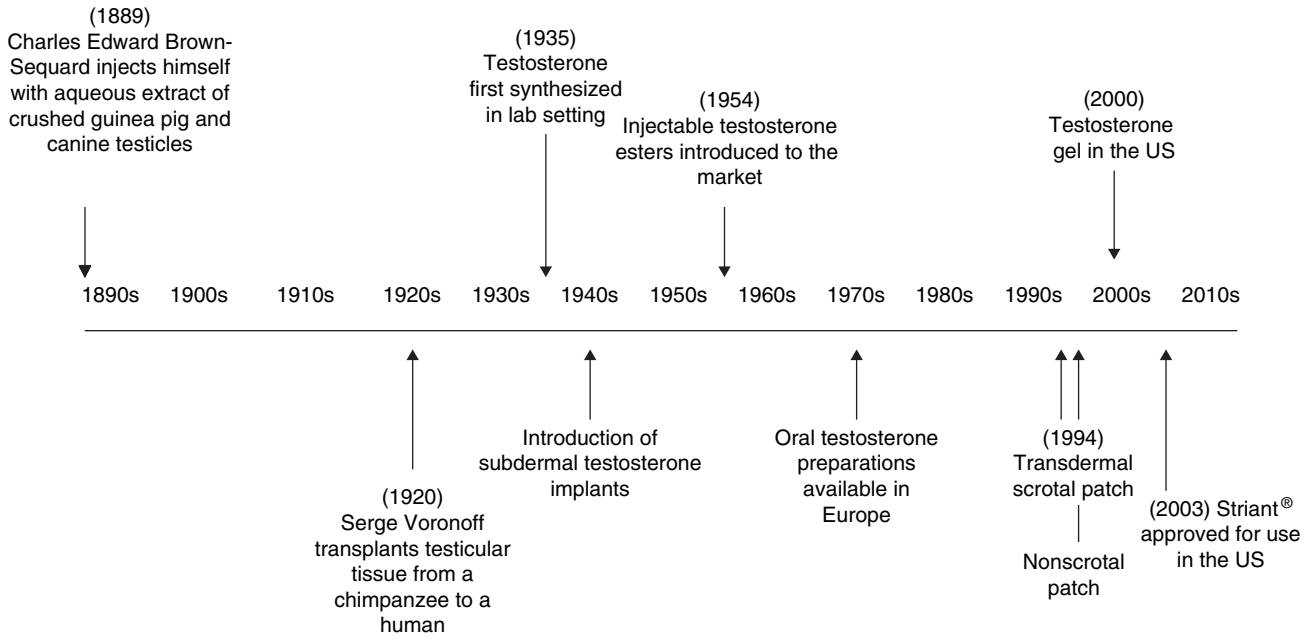

Figure 1. History of testosterone replacement therapy.

Adapted from Neischlag E, Behre HM, Bouchard P *et al.* Testosterone replacement therapy: current trends and future directions. Hum Reprod Update 2004;10(5):409-19 [4].

increased to 81.8% when treated with the patch [10]. In addition, a meta-analysis showed that 80.9% of men had improved erectile dysfunction with the patch, while only 51.3% with intramuscular injection and 53.2% with oral forms demonstrated improvement [11].

These patches offer the benefit of recreating the normal circadian rhythm of testosterone and dihydrotestosterone (DHT) in the male, and demonstrate a lower DHT:testosterone ratio than the scrotal patches [12]. Unfortunately the patches can be expensive. Side effects can be problematic with skin irritation (sometimes relieved by pre-treatment with 1% triamcinolone acetonide cream [13]), skin induration, vesicle formation, contact dermatitis, and headache and depression.

3.1.2 Gel preparations

In 2000 testosterone gel was introduced to the market and became a popular choice for many patients. The gels (Androgel® or Testim®) come in 5 and 10 g tubes and are mixed with a skin permeation enhancer and ~ 67% ethanol by volume. They are applied in the morning to the shoulders, abdomen, or upper arm, preferably at the same location every day, drying on the skin within 10 – 15 min. Anywhere between 9 and 14% of the testosterone in the gel is bioavailable and reaches steady-state systemic concentrations within 48 – 72 h. For one dose about 10% is absorbed within 24 h, demonstrating a two- to threefold increase in serum levels after 2 h and increasing to four- to fivefold after 24 h [14]. Of note, DHT and estradiol levels follow the same pattern. Since the dermis contains the 5α-reductase enzyme, which converts testosterone to DHT, all forms of transdermal testosterone replacement produce normal or elevated levels of DHT [10,12,15,16].

Similar to the patch preparations, the gel offers the benefit of multiple levels of dosing that can be tailored to the patient's individual needs. In addition, the two gel preparations differ in pharmacokinetics. Testim® contains pentadecalactone, an agent that enhances absorption but also has a unique odor and possible skin reaction [17] which is not tolerated by some. However, patients on Androgel who do not achieve normal testosterone levels may try Testim if they wish to continue using a gel formulation [18]. Local skin irritation occurs much less frequently than with patches (5.5 vs 66%, respectively), thereby increasing compliance [19]. Side effects include acne, headaches, emotional lability, as well as nervousness, gynecomastia, mastodynia, insomnia, hypertension, hot flushes and polycythemia. Patients may also be concerned about interpersonal transfer of the gel to loved ones, however, one study concluded that washing the gel 10 min post-application does not decrease absorption and that transfer is insignificant [20]. However, it is still recommended by the producers of Testim that patients wait 2 h post-application before showering and by the producers of Androgel that patients wait 5 – 6 h.

3.2 Oral replacement

3.2.1 Testosterone undecanoate

Oral testosterone became available for patients in the 1970s in Europe, although it has not yet been approved for use in

Table 1. Agents available for the treatment of male hypogonadism.

Testosterone options	Doses	Advantages	Disadvantages
Topical			
Patches			
Scrotal			
Testoderm®	4-mg and 6-mg patches, applied daily	Greater improvement of erectile dysfunction over intramuscular and oral forms	Expensive Skin irritation, skin induration, vesicle formation, contact dermatitis, headache, depression
Nonscrotal			
Androderm® Andropatch®	5-mg and 2.5-mg patches which can be combined; replaced nightly	Recreation of normal circadian rhythm	
Gels			
Androgel® Testim®	5 – 10 g/day	Skin irritation less common that with patch	Acne, headache, emotional lability, nervousness, gynecomastia, mastodynia, insomnia, hypertension, hot flushes, polycythemia
Oral			
Ingestible tablets			
Testosterone undecanoate Andriol®	120 – 240 mg/day (40 – 80 mg t.i.d.), to be taken with a fatty meal	Demonstrated safety	Erratic bioavailability Frequent dosing
Transbuccal			
Striant®	One 30 mg tablet, b.i.d.	Avoids first pass metabolism	Unpleasant taste Tolerability
Injectable			
Testosterone esters			
Testosterone cypionate Testosterone enanthate Testosterone propionate	200 mg every 2 – 4 weeks 200 mg every 2 – 4 weeks 10 – 25 mg 2 – 3 × per week, not to be used on a long-term basis	Relatively inexpensive	Invasive, painful, risk of hematoma and local skin-site reaction Polycythemia, acne, nonproductive cough, gynecomastia
Testosterone undecanoate			
Nebido®	1000 mg every 12 weeks following a 6-week loading dose	Serum testosterone levels consistently in physiological range Four injections per year	Concern for effects on prostate
Surgical Implants	4 – 6 200-mg implants, lasting up to 6 months	Treatment only twice per year	Placement is invasive Risks of extrusion and site infection

the US. Oral preparations of testosterone esters have significant safety issues and inconvenient dosing [21]. Testosterone undecanoate, however, has proved effective in the oral form for the treatment of hypogonadism. For proper uptake into the system, oral testosterone undecanoate must be taken with a fatty meal. It is absorbed into the lymphatics and then travels to the bloodstream, bypassing first-pass degradation in the liver. Peak levels can be measured in the bloodstream 2 – 6 h post-administration. Doses are typically 120 – 240 mg/day [22,23].

The response to treatment with the oral preparation is somewhat variable. However, in a double-blind crossover study of 160 mg/day of oral testosterone undecanoate (TU), several patients did not reach normal levels, although the majority of patients experienced moderately increased serum testosterone levels [24]. Of note, DHT was increased to a greater degree than testosterone. Oral TU has proved successful in treating hypogonadal males over a period of 60 days and led to improved sexual interest and ejaculation. It has also been proven to result in an increase in lean body

mass and a decrease in muscle fat in a year-long trial of healthy males over the age of 60 [25]. TU has demonstrated safety and could be considered a suitable option for mildly hypogonadal men, but likely will continue to require three-times daily dosing.

3.2.2 *Transbuccal preparation*

A slightly different option recently introduced to the market is the transbuccal preparation (Striant®). This option also avoids first-pass hepatic metabolism by absorption directly into the buccal mucosa and circulation therein. Each tablet is 30 mg and rapidly adheres to the mucosa, forming a gel. Food and beverage intake does not affect absorption. Serum testosterone levels peak 30 min after application and closely parallel rises in DHT and estradiol [26,27].

In a comparison study with the patch, 84.8% of patients treated by the transbuccal system achieved normal testosterone levels, while only 55.1% did so with the patch [28]. In another study, 92.3% of patients achieved normal testosterone levels with the buccal system while only 83.3% of patients using testosterone gel achieved levels in the normal range [27]. In addition, due to the presence of 5-alpha reductase enzyme in the skin, the gel created higher levels of DHT in patients than did the buccal system. Side effects include reactions at the site of application (including gingivitis, edema and blistering), as well as a bitter taste, xerostomia, toothache, stomatitis, anxiety and stinging of the lips. However, the transbuccal preparation is generally well tolerated, and 60% of patients in one study, when given the option, chose to continue using the preparation for a long-term follow-up study [29].

3.3 Injectable preparations

3.3.1 *Testosterone esters*

Injectable testosterone first came to the market in the 1950s with the development of testosterone esters (TE). These esters include testosterone propionate, testosterone enanthate and testosterone cypionate. Esterification of testosterone at the 17β-hydroxy position makes the molecule more hydrophobic and creates a longer duration of action. Emulsification of the testosterone ester in an oil carrier further increases half-life of the product. They are relatively inexpensive, although they require deep intramuscular injection and frequent administration. Testosterone cypionate and testosterone enanthate must be injected every 2 – 4 weeks and testosterone propionate 2 – 3 times per week. For this reason testosterone propionate is not to be used on a long-term basis.

In general, testosterone in the serum reaches supraphysiologic levels 24 h after a 200-mg injection of the two longer-acting testosterone esters above, followed by a gradual decline in the serum to hypogonadal levels over the following two weeks. Because the pharmacokinetics vary, these preparations can cause mood swings and variability in libido, sexual function and energy levels in the individual patient. The deep injections can be painful and lead to hematomas, injection site reactions and pruritus, as well as the more systemic reactions of polycythemia, acne, nonproductive cough and gynecomastia [9,10].

3.3.2 *Testosterone undecanoate*

More recently a new, even longer acting testosterone ester has entered the market and appears to be a solution to many of these problems. TU (Nebido®), discussed above in the context of oral administration, is available as an injectable form (in Europe, expected approval for use in the US in 2008). Its increased half-life in comparison to the other esters is due to its longer hydrophobic side chain (11 vs 7 carbon atoms). TU is injected with a castor oil carrier which further improves its duration of action over preparations in tea seed oil [30]. A dosing regimen of 1000 mg every 12 weeks following a 6-week loading dose has been suggested. Studies show a 12-week interval between doses to be safe and effective (without severe oscillations in serum testosterone levels) over a 3-year period. In addition, this same trial demonstrated that patients could be transitioned from TE to TU without interruption in their treatment [31]. Multiple studies show that serum testosterone levels are consistently maintained within the normal physiological range [23,32]. Hypogonadal men on this treatment regimen would therefore receive four doses a year rather than the standard 26 with the other esters on the market; a much more attractive option to many patients.

Patients on TU benefit from an increase in lean body mass, improved emotional stability [33] and sexual function, as well as decreased total cholesterol. In addition, patients demonstrated a decrease in serum high density lipoprotein (HDL) and an increase in hemoglobin and erythrocyte counts. Noted side effects include gynecomastia and breast tenderness. Of concern in the elderly population is that PSA and prostate size increased during the course of the studies [34]. Neither exceeded the normal range, however these results may persuade physicians to avoid prescription of intramuscular TU in the aging population. Several studies have been conducted in an effort to refute a possible link between TU administration and prostate cancer, and these will be discussed below under safety considerations.

3.4 Surgical implants

An even longer-lasting option for hypogonadal men is the implantation of crystalline testosterone pellets, available in the UK and Australia. The pure testosterone pellets are inserted subcutaneously and held with a retention suture, and erosion at the surface of the pellet leads to systemic absorption. Typically, four to six 200-mg implants are implanted and last for up to 6 months with mid to high range testosterone levels achieved in the body [35,36]. Adverse effects include spontaneous extrusion at the site of insertion, as well as other surgical side effects such as infection.

The procedure is relatively invasive and may be unattractive to patients because of this. Compliance and reliability have not been assessed long term, and this option should probably only be used in younger men because of the obvious possible risks to the aging male [37].

3.5 In development

Several products are undergoing development or are in phase I trials currently. Development is aimed at creating drugs that can be used with long dosing intervals (such as testosterone undecanoate) and those that are tissue specific, to avoid unwanted side effects. These will be summarized below (as reviewed by [32]).

3.5.1 5α-dihydrotestosterone

Currently available outside of the US, this product comes in a gel form that is applied to any large area of skin and creates a steady-state serum concentration within 2 – 3 days of starting applications. Because DHT is not converted to estrogen, it should not affect men with gynecomastia or microphallus. Concerns regarding effects on the prostate are reasonable, considering that DHT is normally responsible for prostate growth. However, trials demonstrate improvements in sexual function and increased lean body mass without significant prostatic effects, and one trial actually demonstrated a paradoxical decrease in prostate volume [38].

3.5.2 SARMs

Selective androgen receptor modulators (SARMs) are a popular area of research and development due to their potential for tissue specificity. They do not undergo aromatization or 5α-reduction and so it is hypothesized that they will have minimal to no effects on the prostate or the cardiovascular system. Yet they would potentially still increase lean body mass, bone mass, libido and virilization.

Animal studies have demonstrated promising results and helped to strengthen the hypothesis of the tissue specificity of these agents. Phase I trials are currently being conducted with SARMs for hypogonadism treatment, and several new compounds are being developed for testing. The data thus far are promising [39].

3.5.3 SERMs

Clomiphene citrate, a selective estrogen receptor modulator, is in Phase III clinical trials for the treatment of secondary male hypogonadism. It is believed to compete with estradiol at the hypothalamus, blocking negative feedback and thereby increasing GnRH release and subsequent testosterone production. This can be noted by observing some of its downstream effects [40]. In a recent trial with 178 patients, 75% had significantly increased sexual function and gonadotropin levels, with the greatest benefit seen in younger patients and those with anxiety disorders. Older men with comorbidities did not respond as well [41]. A more recent study of 36 men in a 3-month trial demonstrated clomiphene's efficacy in increasing serum testosterone levels, however no long-term safety data is yet available [42].

3.5.4 7α-methyl-19-nortestosterone

Also known as MENT, 7α-methyl-19-nortestosterone is a compound with 10 times the potency of testosterone and a faster clearance as it is not bound by SHBG. MENT does not undergo 5α-reduction but is still aromatized to estradiol, and therefore is somewhat tissue specific. It has been demonstrated to enhance sexual function with a blunted effect on prostate growth compared to testosterone [43]. High-dose MENT, however, has been shown to increase prostate volume and actually lead to a decrease in lean body mass in orchiectomized rats [44]. It therefore will be necessary to optimize the dose of this compound in order that it may be a suitable alternative for aging men who are at increased risk for benign prostatic hyperplasia and/or prostate cancer.

3.5.5 Aromatase inhibitors

By blocking the enzyme aromatase, these inhibitors block the production of estradiol. Although this enzyme is found throughout the body, it is most abundant in adipose tissue and plays a key role in creating estradiol for negative feedback on the hypothalamic-pituitary-gonadal axis. Aromatase inhibitors block the negative feedback mechanism resulting in a greater production of endogenous LH and testosterone. A study in older males (ages 62 – 74) with the product anastrozole demonstrated increased serum total and serum bioavailable levels of testosterone levels with minimal effects on prostate enlargement [45]. In another study, testosterone:estradiol ratio was increased by administration of anastrozole, thereby increasing sperm motility and density [46].

3.5.6 hCG

Human chorionic gonadotropin is a player in the hypothalamic–pituitary–gonadal axis that binds to receptors on the Leydig cells, stimulating testosterone production. It comes in an injectable form and 1000 – 2000 IU of intramuscular or subcutaneous administration two to three times per week has demonstrated efficacy in increasing serum testosterone levels. In addition, it can stimulate testicular spermatogenesis [47]. Other studies have demonstrated that a recombinant human form has increased muscle mass, although there were no effects on muscle strength or functioning. No significant effects were demonstrated regarding PSA, hematological measures, or sexual activity [48]. Side effects are few and include nipple tenderness and injection site discomfort. Long-term studies are needed for further data.

4. Safety issues

While testosterone replacement therapy is an attractive option for many men, providers must always consider the potential ramifications of therapy. As we have seen above, the side effects of different therapies vary, and those side

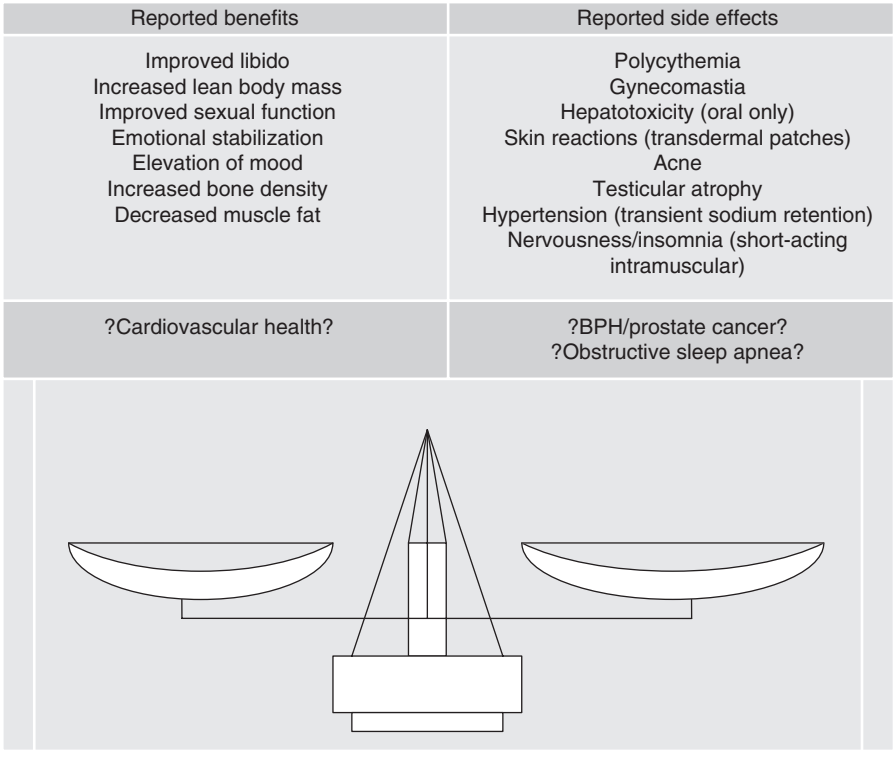

Figure 2. Weighing the benefits and risks of therapy.

effects are more or less permissible depending on the age and risks of the patient population. Potential side effects include cardiovascular disease, lipid changes, erythrocytosis, fluid retention, increased prostate size and prostate cancer, hepatotoxicity, sleep apnea, gynecomastia, skin reactions, acne and testicular atrophy (see **Figure 2**). Clearly some of these are more severe than others, and the data behind several of these effects will be considered below.

As men in general have more cardiovascular events than women, it has been proposed that higher serum testosterone levels may be linked to cardiovascular risks. However, studies demonstrate that higher levels of testosterone are neutral or even beneficial in this area. A study including men undergoing coronary angiography found no correlation between endogenous testosterone levels and coronary artery disease [49]. Another study reviewing previously performed angiography and testosterone levels found that men with coronary artery disease had lower testosterone levels [50]. In relation to testosterone supplementation therapy, trials have demonstrated that with supratherapeutic replacement, men had a transient activation of the hemostatic system including increased antithrombin III and prothrombin fragment F1.2 and decreased protein C, free protein S, and plasminogen activator inhibitor [51]. Laboratory work corroborates a role for androgens in the cardiovascular system by demonstrating a direct effect of testosterone on vascular endothelial cells [52]. Based on several reports indicating that men with diabetes and metabolic syndrome are more likely to have low testosterone levels [53-55], one could postulate an association between testosterone and decreased cardiovascular risk. The effects of long-term therapy will require further studies.

As mentioned above, some testosterone replacement modalities have demonstrated a reduction in HDL (including high intramuscular doses of testosterone undecanoate), however usually with a concurrent reduction in total cholesterol levels. Other information from reviews and meta-analyses suggests a neutral effect of testosterone replacement on serum lipid values in hypogonadal men [56].

Higher testosterone levels have been correlated with polycythemia. Adult men in general have higher hemoglobin levels than adult women and hemoglobin levels rise in the adolescent male as he undergoes increased testosterone release during puberty. Increases in blood viscosity can have serious effects, including aggravation of coronary artery disease or atherosclerosis. Intramuscular preparations appear to confer a higher risk of stimulating erythropoiesis than transdermal preparations, although transdermal preparations have been shown to increase erythrocytosis in a dose-response manner [19,57]. Thus, hemoglobin and hematocrit should be monitored in men undergoing testosterone replacement therapy and treatment modified accordingly. In addition, there is controversy as to whether or not testosterone replacement is associated with obstructive sleep apnea (OSA) [58,59]. As OSA is also linked with erythrocytosis and

the so-called 'Pickwickian Syndrome,' it represents a possible confounding variable, although at least one study suggests that sleep apnea is likely to be a problem with supraphysiologic replacement [60].

One major concern for elderly patients initiating or continuing therapy is the risk of benign prostatic hypertrophy (BPH) and/or prostate cancer. Having heard that androgens are required for prostate growth, it is an understandable and logical concern. In addition, castrated animals show a decrease in prostate volume, and men with prostate cancer often undergo treatment to reduce testosterone levels. Several case reports detail incidences of prostate cancer in men undergoing prostate replacement therapy, although it is not possible to prove causality in these cases [61,62]. However, in multiple trials where testosterone is replaced to physiologic levels, neither prostate volume nor prostate specific antigen (PSA) increased above normal values. In fact, one study found that men with lower serum testosterone levels had worse disease, as measured by Gleason scores [63]. Urinary retention symptoms are not increased above those taking placebo. One compilation of studies of men on testosterone replacement therapy demonstrated a prostate cancer incidence similar to the general population, and a case-control study of 204 individuals demonstrated that in fact patients with prostate cancer have lower levels of androgen bioactivity than controls [64]. However, in another study, higher levels of serum free testosterone were found to be associated with an increased risk of prostate cancer in a retrospective analysis [65]. Despite fluctuations in results between studies, the large majority of studies to date demonstrate no correlation between increased testosterone levels and increased incidence of prostate cancer [66,67].

With the above information in hand, it is still necessary to continue routine prostate screening examinations in those men treated with testosterone replacement therapy. PSA levels should be tested regularly in conjunction with performance of digital rectal examination, and a low threshold for prostate biopsy is recommended. In the past, a history of prostate cancer precluded a patient from receiving testosterone replacement therapy, although this guideline is now under debate. Two studies exploring testosterone replacement therapy in men with organ confined prostate cancer who underwent radical prostatectomy demonstrated no recurrence, suggesting that not all men with a history of prostate cancer should have testosterone replacement therapy withheld, at least in the short term [68,69]. Perhaps the advent of new tissue-specific androgen replacement therapies will allow physicians to circumvent this issue.

5. Published therapy guidelines

A number of guidelines have been proposed for practitioners treating hypogonadal men. Of particular interest are the guidelines set forth by a task force of the Clinical Guidelines Subcommittee of the Endocrine Society [70] outlining several suggestions and recommendations. For instance, they do not recommend screening everyone who comes in for a routine exam, but rather only those who demonstrate signs and symptoms related to hypogonadism. Testosterone levels should be tested in the morning and confirmed, if necessary, with assays for levels of bioavailable testosterone. Contraindications to therapy include patients with breast or prostate cancer, a palpable prostate nodule, induration, or PSA level greater than 3 ng/ml, erythrocytosis, untreated OSA, and class III or IV heart failure, among others. Monitoring of patients who are being treated is of extreme importance, and the Endocrine Society suggests aiming for mid-normal levels of testosterone.

6. Conclusion

Hypogonadism is an increasingly recognized phenomenon that requires further attention. As the number of elderly individuals in the population rises, treatments for the age-related decline in testosterone levels will become increasingly important. Currently available treatment options include oral and buccal preparations, transdermal patches and gels, implantable pellets and intramuscular injections. With the recent advent of injectable testosterone undecanoate, males may have the convenient option of four intramuscular injections per year to restore normal hormonal levels. In all forms of testosterone replacement, potential benefits include increased lean body mass, heightened libido, increased bone density and elevation of mood.

However, with this treatment comes the potential for risk. While certain side effects of the preparations are clear (i.e., skin reactions with dermal preparations, poor taste with buccal preparations, erythrocytosis with intramuscular injections), others are less so and warrant further investigation (i.e., the effects of testosterone replacement therapy on prostate cancer risks and development). Because of these potential risks, alternate preparations are currently undergoing research and development, with the hope of developing long-lasting, convenient, tissue-specific preparations that will reduce the side effect profile of replacement therapy.

Suggested therapy guidelines include monitoring serum testosterone levels with therapy, regular check-ups for prostate health, and watching for serious side effects in individual patients. Prostate health screening is of the highest importance in the aging male, who is already at increased risk for prostate cancer by virtue of age alone. As testosterone replacement therapy becomes an increasingly frequent aspect of treatment, it will be important that this information be emphasized to current and future physicians.

7. Expert opinion

There is an abundance of testosterone delivery systems available on the market, providing a wide range of options for both practitioner and patient. In addition, there are clear

advantages to one delivery system over another in individual patients. For example, one would perhaps avoid the use of a transdermal preparation in a patient with psoriasis, or an intramuscular preparation in a patient with hemophilia. Other decisions can be left to patient preference: some males may be unable to tolerate the presence of the transbuccal preparation, while others find its self-administration a convenient option. Therefore most of the decision in choosing a testosterone application system should rely on conversation between doctor and patient, taking into consideration patient preference given known side effect and efficacy profiles.

However, there are a number of areas in testosterone replacement that remain ambiguous. The most intriguing area of controversy remains on the subjects of BPH and prostate cancer. We believe that there is not yet enough evidence to support or refute a role for testosterone replacement therapy in the development of BPH and prostate cancer in the aging population. It remains unclear whether men who are at increased risk for prostate cancer by virtue of their advanced age could increase their risk of cancer development by increasing serum testosterone (and DHT) levels. Here we have cited studies above describing a similar incidence of prostate cancer among individuals of comparable age who are taking testosterone supplementation to achieve normal serum testosterone levels and those who are not. Still, case reports of men developing prostate cancer while taking testosterone remain concerning for prescribers, however incidental they may be. In general, the authors believe that with careful monitoring, testosterone replacement is safe and should not be withheld due to the fear of prostate cancer. In a man at risk for prostate cancer, short-acting testosterone agents such as patch/gel preparations might be advantageous, in combination with regular prostate exams and PSA levels, so that therapy may be withdrawn if gland hypertrophy or nodularity is noted or PSA levels rise beyond expected levels. This is in keeping with the recommendations set forth by the Endocrine Society.

Long-acting forms of treatment, such as injectable testosterone undecanoate, have great promise to improve compliance for the hypogonadal man. The convenience of its administration and its proven benefits make it appear to be an ideal replacement therapy for individuals, particularly for the younger man requiring testosterone replacement for life. One might also be more willing to continue testosterone replacement therapy into old age in these individuals, continuing to monitor for any signs of cancer development. However, prescribers should keep in mind that more long-term studies need to be conducted with this product to ensure its safety.

There still remains an opportunity to develop a testosterone replacement option that is more end-organ specific and able to selectively treat the testosterone deficiency, i.e., a product more effective at the level of the bone or muscle, but not prostate. There is a great need for continued research and development in the area of hypogonadism as our aging and co-morbid populations continue to grow.

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