Testosterone Replacement Therapy in Men: Effects on Fertility and Health

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4.1 Introduction

A rising volume of the current literature has demonstrated the safety and health benefits of testosterone replacement therapy for late-onset hypogonadism in men. The simultaneous increase in the coverage both by the lay media and the internet has allowed public awareness of the notion of "andropause" to growth tremendously. As a result of this growing demand from patients for evaluation, counseling and treatment of late-onset hypogonadism along with the increased knowledge, comfort levels, and willingness of healthcare professionals in managing the condition [1], the number of prescriptions of testosterone replacement therapy (TRT) has exploded in the past decade. The levels of sales of TRT products were estimated to have increased by 500 % from 1993 [2]. In a comprehensive global report on TRT market, Global Industry Analysts projected the global TRT market to reach $5.0 billion in 2017. In response to such a paradigm shift of late-onset hypogonadism management resulting in a rapidly growing consumer market, the pharmaceutical products available for testosterone replacement therapy not only have increased in their varieties but, more importantly, have also undergone significant modifications on various aspects such as the improvement of safety, bioavailability, and cost-effectiveness. A growing volume of the adult male population is expected to be on testosterone replacement, possibly as a life-long therapy for hypogonadism. The focus of this chapter is on the use of testosterone replacement therapy for late-onset hypogonadism in men and its potential impact on the general and reproductive health.

4.2 Hypogonadism in Adult Male

Clinically, male hypogonadism refers to the state of health where there is a deficiency of androgen activity. Male hypogonadism may be due to intrinsic testicular failure in testosterone production and spermatogenesis, a condition commonly referred to as primary hypogonadism. On the other hand, when hypogonadism is caused by inadequate gonadal stimulation from the hypothalamus–pituitary axis production and release of gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), it is referred to as secondary (or central) hypogonadism. Other medical conditions such as hemochromatosis, diabetes, severe malnutrition, and febrile illnesses may also interfere with normal gonadal function leading to hypogonadism [3].

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Table 4.1 Presentations of late-onset hypogonadism in men

Erectile dysfunction
Decreased sexual desire
Mood changes
Cognition/memory impairment
Lack of energy/motivation
Sleep disturbances
Quality of life
Anemia
Dyslipidemia
Sarcopenia
Loss of body hair (axillary and pubic)
Loss of height
Osteopenia/osteoporosis
Low-impact fracture
Loss of muscle mass
Decrease in physical strength and performance
Hot flushes
Testicular hypotrophy
Central obesity

Of note, secondary hypogonadism may be congenital and iatrogenic. Idiopathic hypogonadotropic hypogonadism (IHH) with normal sense of smell (normosmic) or with anosmia (Kallmann syndrome) is a rare genetic disorder caused by an isolated defect in the secretion of GnRH (gonadotropin-releasing hormone) by the hypothalamus, or, less frequently, by a defect in the action of GnRH on pituitary gonadoropes [4]. Iatrogenic causes of secondary hypogonadism include surgical removal of the pituitary gland for treatment of tumors such as craniopharyngioma and pituitary adenoma. Traumatic damage to the pituitary gland is another cause of secondary hypogonadism. In these cases where the direct cause of hypogonadism is specifically secondary to gonadotropins deficiency, replacement therapy with gonadotropins or GnRH (for IHH) is an established effective therapy to resume gonadal function for both spermatogeneis and testosterone production.

Our focus of discussion, however, will be on late-onset hypogonadism (LOH) for which the common choice of pharmacological management is replacement therapy with testosterone or testosterone-based products. LOH refers specifically to a cluster of presentations (Table 4.1) that appeared in adulthood secondary to a decline in androgen activity. Various studies have indicated a gradual decline in serum testosterone levels in men with increasing age. In the media, this condition is often referred to with the laymen's terms "andropause" or "man-opause" (as an anology menopause in female). Other more precise terms used to describe this syndrome include testosterone deficiency syndrome (TDS) and partial androgen deficiency in aging men (PADAM).

4.2.1 Insulin Resistance

Serum testosterone levels decline 1–1.5 % per year after age 30 years [5]. At the level of the hypothalamus, pulsatile release of GnRH is thought to be reduced in quantity with old age with possible loss of the circadian rhythm. At the testicular level, Leydig cell response to GnRH is also blunted with aging. This, combined with increase of the levels of sex hormone binding globulin, results in decrease in the free level of testosterone. The true prevalence of hypogonadism varies in different reports depending on the age group, health status, ethnicity, and other factors [6]. The Massachusetts Male Aging Study demonstrated that the prevalence of hypogonadism in men ranges from 6.0 to 12.3 % between the ages of 40 and 69 years and estimated that 2.4 million men in the USA have androgen deficiency [7]. A more recent report estimated the prevalence of low testosterone (serum total testosterone < 300 ng/dL or 10.4 nmol/L) to be as high as 38.7 % in males over the age of 45 in outpatient primary care populations [8].

Hypogonadism has also been linked to general health conditions such as dyslipidemias [9], type II diabetes [10–12], metabolic syndrome [13], and even increased mortality. Shores et al. [14] followed over 800 male veterans for an average of 4.3 years and found that low serum testosterone was associated with higher all-cause mortality. Similar conclusions was drawn by Khaw et al. [15] who followed over 11,000 men aged 40–70 year for 10 years and reported the associated risks of low endogenous testosterone

with elevated risks of all-cause mortality, cardiovascular-related mortality, and cancer-related mortality. Men in the highest quartile testosterone levels were found to have 30 % reduction in mortality compared with those in the lowest quartile. In an epidemiologic model developed to quantify the impact of hypogonadism (using a prevalence of 13.4 %) as a predisposing factor for men's health, Moskovic et al. [16] determined that, over a 20-year period, hypogonadism is projected to be involved in the development of approximately 1.3 million new cases of cardiovascular disease, 1.1 million new cases of diabetes mellitus, and over 600,000 of osteoporosis-related fracture, with an attributed cost burden of these diseases estimated to be $190–$525 billion in inflation-adjusted healthcare expenditures in the USA.

4.3 Benefits of Testosterone Replacement Therapy on General Health

Since the first published case in Lancet in 1889 by Dr. Charles Brown-Sequard on self-injection of testicular extracts from animals resulting in increased energy, muscle strength, stamina, and mental agility [17], a wealth of literature, particularly from the past three decades, has reported various general health benefits of various forms of testosterone replacement therapy (TRT) on men with hypogonadism. Controversies do exist on whether TRT is efficacious in providing benefits to men with late-onset hypogonadism on various health issues. Since most of the current interventional studies are short term and non-placebo controlled with heterogenous baseline parameters and different designs in the outcome measured and analyzed, it is challenging to delineate what subgroups of patients will have the maximal benefits of TRT to have long-lasting improvement on the various aspects of their general health. Ideally, large-scale, multicentered, long-termed randomized, placebo-controlled trials are needed to fully establish not only the long-termed efficacy but also the potential health risks of TRT. A new multicentered clinical trial, sponsored by The National Institute on Aging of the National Institutes of Health of the United States, is expected to complete by mid-2015 (http://www.clinicaltrials.gov/ct2/show/NCT00799617?term=testosterone+aging&rank=40) and should provide more definitive answers to potential benefits of TRT in aging men. However, it is not powered to assess all potential risks such as prostate cancer and cardiovascular events [18]. Thus, clinicians should be cautious in drawing their conclusions using the evidence-based results available from the current literature. Various clinical recommendations and guidelines have recently been published by reputable societies of interest on the evaluation, counseling, management, and monitoring for men with late-onset hypogonadism [19–21].

4.3.1 Fat and Muscle Composition

Increase in lean muscle mass, particularly in the trunk, along with decrease in fat mass in the extremities, have been reported with TRT in elderly men [22, 23]. The translation of these positive effects of TRT on muscle strength, motor performance, and fall prevention, however, is controversial [24]. In men with significant comorbidity such as chronic obstructive pulmonary disease [25], men receiving glucocorticoids [26], and frail and elderly men in rehabilitation [23, 27–29], improvement in muscle strength or physical function after TRT has been reported. In healthy elderly men, on the other hand, three randomized, placebo-controlled trials with 6 [30] and 36 months [22] of treatment failed to demonstrate improvement in muscle strength.

4.3.2 Bone Composition

Hypogonadism is a known cause of osteoporosis and osteopenia. Rapid bone loss is observed after castration and androgen deprivation therapy [31]. Bone microarchitecture and cortical and trabecular bone mineral density are impaired in men with hypogonadism [32], resulting in increased risks of bone fractures [33, 34]. The prevalence of

hypogonadism was found to be ~60–70 % in men with hip fractures [35–37] and up to 20 % in men with vertebral fracture [38]. Several interventional studies, including placebo-controlled studies and meta-analyses, reported increase in bone mineral density after TRT for hypogonadism, with greater increase in the lumbar spine than in the hip [24, 39–43]. However, there is currently insufficient data to determine the efficacy of TRT on reducing the risk of bone fracture.

4.3.3 Sexual Function

Reduced libido or sex drive has been associated with hypogonadism [44, 45]. The association of erectile function with serum testosterone levels, on the other hand, is less clear [45–47]. It appears that when it is clearly subnormal (<320 ng/dL or 11 nmol/L), there is a syndromic association with decreased serum total testosterone levels with sexual symptoms such as morning erection, low sexual desire, and erectile function [48]. A recent 6-month randomized controlled trial on TRT in men with testosterone level <395 ng/dL or 13.7 nmol/L failed to demonstrate a benefit on sexual functioning [30]. However, three meta-analyses of published studies including randomized placebo-controlled trials [48–51] revealed improvement on male sexual function with testosterone replacement therapy. The meta-regression analysis [51] demonstrated that the effect of TRT on erectile function was inversely related to the baseline testosterone concentration. Hence, the more severe the hypogonadism, the more significant or impressive are the results obtained with TRT. Minimal or no effect was observed for baseline testosterone levels above 345 ng/dL or 12 nmol/L. Age appears to be another important moderator in evaluating the effect of TRT on sexual function. Boloña [50] reported a sizable and significant effect of TRT on erectile function in trials including young patients and a minimal and nonsignificant effect in those including older ones (mean age > 50 years). One presumable explanation for this observation is that hypogonadism in younger patients may be a main cause of sexual dysfunction while for older men it may be one element of a multifactorial sexual dysfunction. The beneficial effects of TRT on sexual function are also seen in studies on the combined used of testosterone and phostphodiesterase-5 inhibitors (PDE5I's) for erectile dysfunction. These studies [52–56] demonstrated that the addition of TRT can salvaged 37.5–92 % of subjects who failed to respond to PDE5I's alone.

4.3.4 Mood and Quality of Life

Hypogonadism is associated with depressive symptoms, impaired cognitive function, and symptoms of dementia [19, 57–59], though such an association is weak. In a recent systemic meta-analysis evaluated seven placebo-controlled, randomized trials ($n=364$) comparing testosterone replacement with placebo in depressed men, Zarrouf et al. [60] reported a significant positive response to TRT in hypogonadal patients. TRT is beneficial on mood only in men with clear subnormal testosterone levels [61]. But for hypogonadal with severe depression, the benefits of TRT on depressive symptoms seem less significant. In a recent placebo-controlled trial, Pope et al. [62] failed to show any benefit of TRT in depressed hypogonadal men (serum total testosterone<350 ng/dL or 12.1 nmol/mL) who were resistant to selective serotonin reuptake inhibitor as a standard antidepressant treatment.

The results of randomized controlled trials on the effects of TRT on quality of life, as assessed by various questionnaires, yield mixed results. In a 6-month TRT trial with 1 % testosterone gel followed by 12 months of open-label follow-up, Behre et al. [63] reported a significant benefit on the health-related quality of life in the TRT group over the controlled group, particularly in the psychological and sexual subscale scores. In another trial from China using 6 months of oral testosterone undecanoate, quality of life measured by the Short Form Health Survey-12 significantly improved in the TRT group [64]. Similar findings were confirmed by in a 12-month trial with intramuscular testosterone undecanoate in Malaysian subjects [65, 66]. Other trials [27, 30] failed to demonstrate a significant improvement in the quality of life of hypogonadal men treated with TRT.

4.3.5 Components of Metabolic Syndrome

Metabolic syndrome, previously also known as syndrome X, has several components as described by the International Diabetes Federation in a consensus worldwide definition in 2006 [67]. These components include: increased triglyceride levels (>150 mg/dL or 1.7 mmol/L), reduced high-density lipid (HDL) levels (<40 mg/dL or 1.03 mmol/L in males), elevated blood pressure (systolic > 130 or diastolic > 85 mmHg), glucose intolerance (fasting plasma glucose > 100 mg/dL or 5.6 mmol/L), and central obesity. Hypogonadism is common in men with type II diabetes or metabolic syndrome. Men with hypogonadism seem to have an increased risk of subsequent development of type II diabetes and metabolic syndrome. Various studies have reported an inverse relationship between testosterone levels and insulin resistance, dyslipidemia, and central obesity [68, 69]. However, it is uncertain if hypogonadism is a cause or a consequence of metabolic syndrome. Studies have reported that visceral obesity can be a potential cause of hypogonadism but hypogonadism may well be a cause of obesity and insulin resistance [69]. The association of these various components of metabolic syndrome clearly establishes a vicious cycle leading to disease progression.

Several interventional studies demonstrated the beneficial effects of TRT on various metabolic parameters including blood pressure, insulin resistance, lipid profile, body composition, and glycosylated hemoglobin (HbA1c) levels. Isidori et al. [42] reported that TRT in middle-aged men leads to reduction in fat mass and total cholesterol. In a meta-analysis, Whitsel et al. [70] showed a dose-dependent decrease in total cholesterol, low- and high-density lipoprotein-cholesterol. In patients with type II diabetes, TRT was associated with a significant reduction of fasting plasma glucose, HbA1c, fat mass, and triglycerides [71]. For patients with established metabolic syndrome, TRT appears to significantly reduce fasting plasma glucose, Homeostatic Model Assessment (HOMA) index, triglycerides and waist circumference, as well as with an increase of HDL-Cholesterol [69].

4.3.6 Cognitive Function

Barrett-Connor et al. [57] reported high endogenous testosterone, and low estradiol levels predicted improved performance on cognitive function. In short-term interventional studies with TRT, Cherrier et al. [72–74] demonstrated improvements in verbal and spatial memory in healthy men and also in men with Alzheimer disease or mild cognitive impairment. Conflicting results, however, were reported by longer trials [30, 75].

4.3.7 Cardiovascular Function

Current studies by various investigators suggested a link between hypogonadism and increased risks of cardiovascular diseases [76–80]. However, it remains uncertain if low T plays a direct pathogenic role in increasing cardiovascular risks. Hypogonadism may well be a marker of preexisting cardiovascular disease rather than an independent risk factor. The suppressing effects of various chronic diseases including metabolic syndrome and type II diabetes on testosterone levels lead Corona et al. [81] to hypothesize that low T during chronic diseases represents a protective or adaptive mechanism to turn off testosterone-dependent function such as reproduction and physical labor that are less desired when the general physical condition is ailing.

With regard to the effects of TRT on cardiovascular risks, a recent double-blinded placebo-controlled study on men with metabolic syndrome showed that TRT may delay the progression of atherosclerosis, as detected by carotid intima media thickness, and the level of high-sensitivity C-reactive protein [82]. Three meta-analyses [83–85] found no significant benefit of TRT for cardiovascular events. However, the statistical power of these analyses is significantly limited by the small sample series and short duration of study duration. In recent reviews [86, 87], there are over a dozen of recent studies that demonstrated the beneficial effects of TRT on angina with positive effects such as decrease frequency of angina, increase in exercise tolerance, and time

to ischemia. A recent randomized controlled trial [27] of TRT on frail elderly men at the maximum recommended dose of TRT (with 10 mg per day of 1 % testosterone gel) reported a high rate of TRT-associated CV adverse events. This trial, however, was criticized by Morgentaler [88] that: (1) there was no rigorous cardiovascular assessment in the trial where nearly half of the cardiovascular events were self-reported or obtained from outside medical sources; (2) the TRT group had more cardiovascular risk factors at baseline than the placebo group; (3) the cardiovascular events consisted of a wide variety of symptoms and findings that are not specific for cardiovascular diseases such as peripheral edema and syncope. Additional studies are thus required to further evaluate if TRT can truly benefit hypogonadal men in reducing not only cardiovascular risks but also the event-specific mortality rate.

4.4 Side Effects of TRT

4.4.1 Prostate Health

The most significant concern amongst all TRT adverse events is on prostate health. Prostate tissues are androgen responsive. In a case series, Favilla et al. [89] reported that age and total serum testosterone correlate with LUTS as measured by International Prostate Symptom Score (IPSS). But after adjusting for various confounding factors, other studies [90–92] failed to confirm an association between higher serum testosterone levels with worse lower urinary tract symptoms (LUTS). On the contrary, more recent studies demonstrated an inverse relationship between total testosterone, DHT, and the development of LUTS [93, 94]. With regard to TRT, an early meta-analysis in 2005 of randomized, placebo-controlled studies on TRT [84] showed a higher risk in the TRT groups of detection of all prostate events, defined as incidence of prostate cancer, increase in IPSS, increase in prostate-specific antigen (PSA), and acute urinary retention. Subsequently, however, a number of short-term (<1 year) studies demonstrated little negative effect on urinary function or prostate volume (reviewed by Shigehara & Namiki [95]). In fact, several studies, including one randomized controlled trial, demonstrated that TRT may actually improve LUTS [96–102]. It should, however, be kept in mind that most of these studies focused on men with mild to moderate degree of LUTS. For men with severe LUTS (e.g., with high IPSS score above 19 points), TRT remains contraindicated as there exists a risks of increase in prostate volume [99] that may theoretically increase the risks of urinary retention. Further studies including long-term observations and many patients with a wide range of severities of LUTS are required to reach more definitive conclusions of TRT on LUTS.

Prostate cancer represents one of the most commonly diagnosed cancers in men over the age of 40 years. Like normal prostate tissues, prostate adenocarcinoma is also androgen responsive. With the initial report by Huggins in 1941 [103] on androgen ablation therapy causing regression of metastatic prostate cancer, a work for which he was awarded the Nobel Prize for Physiology and Medicine in 1966, it was once thought that TRT would lead to development and progression of prostate cancer. However, an extensive review of the current literature, including several large longitudinal studies of up to 20 years of duration, with over 400,000 men studied, failed to establish a direct link between prostate cancer and high testosterone levels [104]. The most recent placebo-controlled randomized trial of TRT revealed no increase in prostate volume, no change in biomarkers of cell proliferation and angiogenesis, and no increase in prostate cancer cases [105]. A longer trial of TRT for 3 years showed no significant changes in PSA levels beyond 6 months of treatment [22]. A recent trial of over 6 years of TRT showed no relevant changes in PSA concentration, PSA velocity, or any significant prostate cancer risks [106].

For men received TRT with localized prostate cancer treated with radical prostatectomy [107–109], radiation therapy [110, 111], or brachytherapy [112], the risk of biochemical recurrence, as indicated by a significant increase in serum PSA level, was estimated to be 2 of 111 men (1.8 %) [113], not as high as one would

expect should TRT really increase the risks of prostate cancer recurrence. Even for men with untreated low grade localized prostate cancer (Gleason score 6 or 7 out of 10 at initial biopsy), TRT for a median of 2.5 years (range 1.0–8.1 years) was not associated with prostate cancer progression. As Morgentaler [113] stated, although there are as yet no large-scale, long-term controlled studies of T therapy to provide a definitive assessment of risk, numerous smaller clinical trials as well as population-based longitudinal studies consistently failed to support the historical idea that T therapy poses an increased risk of prostate cancer or exacerbation of symptoms due to benign prostatic hyperplasia.

Currently manufacturers for all products for TRT have included statements in product inserts that TRT is contraindicated for men with or suspected prostate cancer. Indeed for men with advanced or metastatic prostate cancer that require androgen ablation, TRT should remain an absolute contraindication (consistent with the conclusion of the original report by Huggins in 1941 [103]). Likewise for men with prostate cancer demonstrating factors of high risk of biochemical recurrence (such as extraprostatic extension, positive margins, or lymph nodes at surgery, Gleason scores of 8 or more on biopsy and invasion of the seminal vesicles), clinician must exercise caution when considering the use of TRT.

4.4.2 Polycythemia

Polycythemia, as indicated by an elevation of hematocrit above 50 %, is the most frequent TRT-related adverse event in most clinical trials. In a meta-analysis of 19 randomized controlled trials with 651 subjects on TRT and 433 on placebo [85], TRT increased the risk of polycythemia over placebo by four times. In a more recent meta-analysis of adverse events, Fernández-Balsells et al. [83] reported that TRT was associated with a significant increase in hematocrit (3.18 %; 95 % CI 1.35–5.01), hemoglobin (0.80 g/dL; 95 % CI 0.45–1.14), and a decrease in high-density lipoprotein (HDL) cholesterol (–0.49 mg/dL; 95 % CI –0.85 to 0.13). Thus, careful monitoring of this parameter to allow dosage reduction or treatment discontinuation is important for all men on TRT.

4.4.3 Gynecomastia

Gynecomastia with or without breast tenderness is a potential side effect of TRT secondary to aromatization of androgens to estradiol which stimulate breast tissue development. Gynecomastia is more commonly seen in elderly men on TRT, probably related to elevated SHBG levels. Though usually transient and may resolves despite continuation of treatment, gynecomastia with breast tenderness can be managed with the addition of antiestrogen such as tamoxifen [114].

4.4.4 Sleep Apnea

Development or worsening of sleep apnea, particularly in obese men or men with chronic obstructive pulmonary disease or smoking history, has been associated with TRT, though most data were from studies using TRT at supraphysiologic doses [115]. Central blunting of CO_2 or increased collapsibility of the upper airway during sleep are some of the suggested mechanisms of sleep apnea exacerbation with TRT [116]. Dose adjustment or discontinuation of TRT or treatment with CPAP for sleep apnea may be considered in managing this complication.

4.4.5 Dermatological Adverse Events

Skin irritation, more commonly with testosterone patch but may rarely occur with other transdermal form, is usually due to skin reaction to the chemicals used for drug delivery. Acne, more common in younger men on TRT, is another dermatological complication secondary to increase secretion of sebum. Management of TRT-induced acne can be managed by good personal hygiene with antiseptic soap. Topical retinoid, benzoyl peroxide, sulfacetamide, or azelaic acid can be

used in more severe cases. Another adverse event of TRT is male pattern baldness that occurs mostly in genetically prone men due to the effects of DHT causing miniaturization on the hair follicles.

4.4.6 Other Adverse Events

Though known breast cancer is an absolute contraindication of TRT, new cases of breast cancer in men treated with TRT remain rare [117]. Flushing of upper body may be due to the action of DHT on the skin and are usually tolerable. Liver toxicity is associated with old testosterone preparation (oral 17-alkylated testosterone derivatives) that is no longer recommended for TRT [19].

4.5 Impact of TRT on Male Reproductive Health

The focus of this section will be on the impact of TRT on male reproductive health through suppression of spermatogenesis. Production of testosterone for clinical use has begun in late 1930s and soon after its effect on male fertility impairment has been recognized [118]. It is thus interesting to see that, in the vast volume of recent publications on hypogonadism management, the negative impact of TRT on male reproductive health is rarely mentioned. Four factors may contribute to this.

First, as mentioned above, testosterone has the effects to enhance sexual function through amelioration of libido or erectile function. Indeed, treatment of sexual dysfunction secondary hypogonadism may lead to increase in frequency of intercourse that is needed for natural fertility. Thus, neither the patients nor treating physicians would intuitively suspect any negative impacts of TRT on male fertility.

Second, many healthcare professionals misunderstood that since testosterone is required for spermatogenesis [119, 120], "extra" testosterone from an exogenous source can only help to further enhance male fertility. Indeed, it is not uncommon to see primary care physicians and gynecologists managing a couple with infertility with low sperm concentration or hypogonadism in the male partners to mistakenly prescribe testosterone hoping to improve their chance of conception. In reality, through negative feedback mechanism, exogenous testosterone will inhibit the release of gonadotropin stimulating hormone and gonadotropins, leading to lack of stimulation of spermatogenesis (and Leydig cells for endogenous androgen production), resulting in impaired fertility and testicular hypo- or atrophy.

Third, there has been a so-called testosterone rebound therapy used since the 1950s for the treatment of idiopathic male infertility [121] in which after testosterone injection therapy resulting in azoospermia, its discontinuation led to increase in semen parameters above baseline with resulting pregnancies. This therapy had misled some clinicians thinking that testosterone is a legitimate treatment option for low sperm concentration. These data, however, did not survive critical assessment and such form of therapy is no longer used since 1980. The observations were likely due to spontaneous fluctuations in semen parameters which, if positive, were wrongly attributed to this "testosterone rebound therapy" [122].

Finally, since the risk of hypogonadism increases with age, most men who are placed on TRT have presumably passed the reproductive age and thus the impact of TRT on spermatogenesis and fertility is considered irrelevant. Indeed, in most interventional studies, even those including subjects below the age of 50 years, semen parameters are generally not part of the outcomes measured. We must, however, keep in mind that in most developed countries, with many couples postponing childbearing until their mid-30s to mid-40s, there is a significant increase in paternal age [123]. Indeed, the birth rates for men aged 20–29 years reached all-time lows in 2009 in the USA while for men aged 40–54 years there has been a steady increase in paternity. Thus, more men who are at risks to develop late-onset hypogonadism and receive TRT will also desire unimpaired fertility, making any potential negative impact of TRT on male reproductive health a timely and relevant health issue.

With the lack of sperm parameters in most interventional studies of TRT on men, our knowledge on the extent of the impact of exogenous testosterone on spermatogenesis is mainly derived from studies on hormonal male contraceptives [124]. The two main functions of testis of testosterone production and spermatogenesis are so closely associated physiologically that it is challenging to interrupt spermatogenesis by hormonal strategies without induction of concomitant hypogonadism with resulting derangement on desirable functions such as libido, potency, and various metabolic processes as described earlier. Exogenous testosterone is, thus, an attractive prototype of hormonal male contraceptive as it can simultaneously suppress gonadotropins to arrest spermatogenesis while maintaining androgenicity.

When extrapolating the results of the various contraceptive studies with native testosterone or other testosterone derivatives to understand their spermatogenic suppression effects, four important points should be kept in mind. First, since native testosterone is rapidly degraded by first-pass metabolism, most of the contraceptive trials relevant to our discussion (i.e., the use of a single testosterone-based drug without combination with other agents such as progestogens) were on chemically modified androgen preparations to achieve a prolonged half-life for a convenient dosing frequency for male contraceptive use. Thus, few studies are done on native testosterone. Second, dosage and/or frequency of the use of these products in these studies may be higher than for general TRT use. Though most contraceptive studies have serum testosterone level monitoring and most subjects had levels within the "normal" range, it is well known that the "normal" serum testosterone range is wide, and most subjects in the trial may be in the higher end of the "normal" range. Third, subjects in these trials tend to be healthy men at younger reproductive ages than typical patients with late-onset hypogonadism requiring TRT. Finally, the availability, contents, and packaging of the various formulations evaluated may vary depending on the legislations of the countries and not all products are necessarily first-line choices of testosterone replacement therapy.

4.5.1 Testosterone Enanthate

Testosterone enanthate was the first testosterone-based product used in large-scale hormonal male contraceptive efficacy study, sponsored by the World Health Organization [125]. An important aspect of many potential male contraceptive methods is that, from the start time of intervention, there is a time lag before a decrease in semen parameters is seen. This lag time occurs for two reasons. First, sperm that have been produced must exit from the testes to the excurrent ductal system and passed by ejaculation. Mechanical contraceptive method like vasectomy is subjected to this lag time. Second, human spermatogenesis cycle of stages may take 2–3 months and therefore, following gonadotropin suppression, a comparable post-intervention lag time is necessary to reach complete spermatogenic suppression. When healthy fertile men were given intramuscularly 200 mg of testosterone enanthate weekly, 70 % reached azoospermia after 6 months. In a subsequent study using 250 mg of testosterone enanthate weekly [126], 98 % of the participants achieved sperm concentration below 3×10^6/mL (taking up to 1 year). For these patients, the contraceptive effect was better than that offered by barrier contraceptive with condoms, with less than two pregnancies per 100 person-year.

4.5.2 Testosterone Buciclate

The World Health Organization's Special Program of Research, Development, and Research Training in Human Reproduction has initiated a testosterone ester synthesis program and identified testosterone buciclate (TB) as the most promising approach to suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Though rarely used for the treatment of hypogonadism at the present time, TB, a long-acting testosterone ester (with a half-life of 29.5 days compared to 4.5 days of testosterone enanthate), can suppress spermatogenesis, reaching azoospermia in three out of eight subjects 10 weeks after a single 1,200 mg injection. Azoospermia has been shown to persist up to 22 weeks [127].

4.5.3 Testosterone Undecanoate

A popular choice of oral formulation for TRT in many countries, testosterone undecanoate was found to suppress spermatogenesis to azoospermia in one out of eight Caucasian subjects at a daily dose of 240 mg over a period of 12 weeks [128]. Due to its short half-life, testosterone undecanoate generally is used orally at multiple daily doses. In a small study with five subjects at 80 mg three times a day for 10–12 weeks, one man became azoospermic, two became oligospermic with sperm concentration below 10×10^6/mL, one had milder degree of sperm concentration decrease, and one showed no change.

Testosterone undecanoate can also be given as 1,000 mg as a depot injection as a TRT. The frequency of dosing is 10–14 week injection intramuscularly. This preparation has been tested as a male hormonal contraceptive at a higher frequency of dosing at 4–8 weeks. In a study on Chinese men with monthly injection of testosterone undeconoate, 11 of the 12 subjects received 500 mg and all 12 subjects of 1,000 mg became azoospermic after 4–6 months of treatment [129]. In a subsequent multicenter efficacy study with over 300 healthy men, 97 % of men achieved azoospermia or severe oligospermia ($<3 \times 10^6$/mL) with an initial loading dose of 1,000 mg followed by monthly 500 mg of testosterone undecanoate injection for 6 months. During another 6 months of efficacy study with continuing monthly 500 mg of testosterone undecanoate injection, only 2 % (6 out of 296) of these subjects had sperm reappear in semen and no pregnancy was achieved. A subsequent 12-month recovery study demonstrated that all subjects had semen parameters returned within the reference range [130]. Though the strong effect of testosterone undecanoate depot injection on suppressing spermatogenesis was further demonstrated in a subsequent phase III clinical trial among Chinese men [131], among Caucasian subject, there appears to be a higher rate of "escape" of complete spermatogenic arrest. Indeed, in an integrated analysis, Liu et al. [132] showed that up to 80 % of Caucasian men vs. up to 90 % of East Asian men suppress sperm output to $<10^6$/mL with androgens, though Caucasian ethnicity predicted faster rates of suppression.

The reasons for the ethnic differences in spermatogenic suppression by testosterone remain speculative [133] and may include: (1) ethnic differences in testicular histomorphometry [134, 135] affecting the intrinsic efficiency of spermatogensis and the response to agents that interfere with the physiological process; (2) differences in hormone concentrations and metabolism of androgen, as demonstrated in various studies [136–146]; (3) differences in CAG- and GGC-polymorphism of the androgen receptor, affecting its activity upon androgen binding [147–150]; and (4) differences in gonadotropin suppressibility [151].

Using 1,000 mg of testosterone undecanoate injection at 6-week interval, 8 of 14 Caucasian subjects achieved azoospermia and an additional 4 of 14 subjects severe oligospermia ($<3 \times 10^6$/mL) at 24 weeks [152]. The authors noted that the extent and kinetics of spermatogenic suppression with injection of 1,000 mg testosterone undecanoate at 6-week intervals is comparable to weekly injection of 200 mg testosterone enanthate. A later pharmacokinetic study concluded that 8-week intervals of 1,000 mg injection would be sufficient for contraceptive purposes [153].

4.5.4 Native Testosterone Pellet

Beside its ester from such as enanthate and undecanoate, native testosterone can also be used as implants inserted surgically under the abdominal skin as a form of TRT to achieve physiological serum testosterone profile with low side effects. McLachlan et al. [154] demonstrated that testosterone implants (800–1,200 mg inserted every 3 months) resulted in suppression of sperm concentration below 1×10^6/mL in 70 % of subjects with no pregnancies ensued over 214 months.

4.5.5 19-Nortestosterone

19-Nortestosterone-hexoxyphenylpropionate represents yet another example of testosterone derivative with longer half-life than testosterone

enanthate as a potential hormonal male contraceptive. Used as anabolic steroid since the 1960s, this 19-nortestosterone ester injected every 3 weeks enabled 10 out of 12 healthy young men to reach azoospermia or severe oligospermia (total sperm count less than 5×10^6) [155], comparable to the effects by testosterone enanthate.

4.5.6 7α-Methyl-19-Nortestosterone

7α-Methyl-19-nortestosterone (MENT) was once considered an ideal option for TRT [156] as it does not undergo 5α-reduction, hence with much lower effect on prostate than on other target organs such as muscle and the pituitary. MENT has tenfold higher potency than testosterone to suppress gonadotropins. In a clinical trial conducted by The Population Council [157] with MENT implant inserted subdermally (each releasing 200–400 μg/day), it was found at 6 months that with two implants inserted, 2 out of 11 subjects became azoospermic and another 2 out of 11 became oligospermic ($<3 \times 10^6$/mL) (none of 12 men with one implant exhibited sperm concentration below 3×10^6/mL). With four implants, 8 of 11 subjects reached azoospermia with one additional subject becoming oligospermic. Upon discontinuation of the drug, subjects with one implant had sperm concentration at or above 20×10^6/mL at 30 days. Recovery time increased at higher doses with a median time to recovery (sperm concentration $>20 \times 10^6$/mL) about 3 months in the four-implant group.

Evidently, there is a considerable risk of spermatogenic suppression with TRT leading to azoospermia, oligospermia, and testicular atrophy, a picture similar to hypogonadotropic hypogonadism. Even for spermatozoa that remain, anomalies in sperm morphology in head and center pieces have been reported in studies on anabolic steroid abuse [158–162]. According to studies on male hormonal contraceptives and anabolic steroid abuse, recovery of spermatogenic function is possible, taking 4–6 months after cessation of TRT but may take up to 3 years or longer [132, 160, 163]. The overall proportion of men recovering spermatogenic function is estimated to be 90 % by 12 months, 96 % by 16 months, and 100 % by 24 months, with East Asian ethnicity predicting a more rapid rate of recovery [132]. Longer treatment studies with more ethnically diverse population (e.g., inclusion of African and Hispanic subjects) are required to fully evaluate the impact of TRT on spermatogenic suppression. For men who clearly desire fertility, treatment of symptomatic hypogonadism with testosterone products should be delayed or avoided. If assisted reproduction is needed, fertility preservation with cryopreservation may be considered before using TRT. Otherwise, various alternative management strategies for late-onset hypogonadism, including lifestyle modification, correction of clinical varicoceles [164], elimination of exposure to drugs and other gonadotoxins, use of antiestrogen or selective estrogen receptor modulator [165, 166], aromatase inhibitors [167], gonadotropin injection [168], or other medical empirical therapies, should be considered when counseling these patients.

4.6 Conclusions

Late-onset hypogonadism is an important men's health issue that has significant negative impact on various aspects of the general health and the quality of life. As the volume of the literature on the various aspects of late-onset hypogonadism and TRT grows, more and more healthcare professionals will adopt an evidence-based approach to diagnose and manage men with the condition. Evidently, questions and controversies do remain on many important aspects of TRT for late-onset hypogonadism, particularly with regard to the various efficacy and safety issues such as the long-term impact of TRT on strength and motor function, prostate cancer risks, improvement in cardiac function, reduction in cardiovascular mortality, and bone fracture rate. Though not frequently included as a point of discussion in most recently published studies on TRT, impairment of male reproductive health through spermatogenic suppression is a timely and relevant issue as men continuing to delay having children until

such age when they are at risk to develop late-onset hypogonadism. Healthcare professionals should, thus, be fully aware of the potential negative health impacts of TRT, in addition to its efficacy, when counseling men presenting with late-onset hypogonadism for the various management options.

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