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MINIREVIEWS

Review of health risks of low testosterone and testosterone administration

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Abstract

Hypogonadism is prevalent in older men and testosterone replacement therapy (TRT) for older hypogonadal men is a promising therapy. However, a number of important clinical concerns over TRT safety remain unsolved due to a lack of large-scale randomized clinical trials directly comparing the health risks of untreated hypogonadism *vs* long-term use of TRT. Meta-analyses of clinical trials of TRT as of 2010 have identified three major adverse events resulting from TRT: polycythemia, an increase in prostate-related events, and a slight reduction in serum high-density lipoprotein cholesterol. There are other purported health risks but their incidence can be neither confirmed nor denied based on the small number of subjects that have been studied to date. Furthermore, subsequent literature is equivocal with regard to the safety and utility of TRT and this topic has been subject to contentious debate. Since January 2014, the United States Food and Drug Administration has released two official announcements regarding the safety of TRT and clinical monitoring the risks in TRT users. Additionally, the health risks related to the clinical presentation of low or declining testosterone levels not been resolved in the current literature. Because TRT is prescribed in the context of putative risks resulting from reduced testosterone levels, we reviewed the epidemiology and reported risks of low testosterone levels. We also highlight the current information about TRT utilization, the risks most often claimed to be associated with TRT, and current or emerging alternatives to TRT.

Key words: Hypogonadism; Epidemiology; Aging; Low testosterone; Testosterone replacement therapy

Core tip: The topic of testosterone replacement therapy which has seen two official announcements for the United States Food and Drug Administration in 2014, is the subject of several large studies both prospective and retrospective, and there is unsettled debate about the safety and efficacy of this treatment. Readers should become familiar with this topic and be aware that further

publications and announcements are likely in the near future.

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LOW TESTOSTERONE EPIDEMIOLOGY AND RISKS

Production of testosterone (T) and serum T concentrations decline as men age. Hypogonadism may be defined either as serum concentration of T (either total T, bioavailable T or free T) or as low T plus symptoms of hypogonadism. The Baltimore Longitudinal Study on Aging reported the incidence of total serum T < 325 ng/dL to be 20% for men in their 60s, 30% for men in their 70s and 50% for men over 80[1]. In an authoritative review by Kaufman and Vermeulen[2] in 2005, similar rates and trends in the reduction of total serum T level were reported. The Massachusetts Aging Male Study reported that 12.3% of men aged 40 to 70 had a total serum T of < 200 ng/dL with 3 or more symptoms of hypogonadism[3]. The Boston Area Community Health Study reported that 5.6% of men aged 30 to 70 were hypogonadal, as defined by total serum T < 300 ng/dL; or, free serum T < 5 ng/dL plus 3 or more symptoms of hypogonadism[4].

Hypogonadism causes a wide range of signs and symptoms including loss of libido, erectile dysfunction, diminished cognitive function, depression, lethargy, osteoporosis, loss of muscle mass and strength[5]. In a literature review on the burden of hypogonadism in adult men, Maggi *et al*[6] demonstrated strong evidence associating hypogonadism with sexual dysfunction and cognitive impairment; and, less compelling evidence associating hypogonadism with depressive symptoms, fractures, and mortality. Several recent studies also reported the health risks associated with untreated hypogonadism, including increased all-cause mortality[7,8], coronary artery disease[9], and stroke[10].

Unfortunately, studying the health risks associated with untreated hypogonadism is often limited by the lack of universally accepted diagnostic criteria, and by study design variations[6].

Hypogonadism does not appear to be identical across racial and ethnic boundaries. In a health screening project among 819 men in Taiwan, the prevalence of hypogonadism (total serum T < 300 ng/dL) ranged from 16.5% for men in their 40s, 23.0% for men in their 50s, 28.9% for men in their 60s, and 37.2% for men older than 70 years of age[11]. The prevalence of hypogonadism among men in Taiwan is higher than the prevalence reported in the Massachusetts Male Aging Study[3], for a similar age group. There are no definitive biological explanations for differences in the epidemiology of hypogonadism. Candidate reasons are related to various lifestyle factors as well as genetic reasons, including the CAG repeat sequence, within the androgen receptor (AR). Rajender *et al*[12] reviewed over 30 studies on the AR trinucleotide repeat and infertility. Overall, for European populations, no significant distinctions were drawn, based on the CAG repeat. However, in Asian populations, four studies indicated a longer repeat was associated with infertility, two indicated no difference was present, and one study reported a shorter length (samples were all oligozoospermic for this subgroup). While there is a suggestion that CAG repeat length may determine androgen responsiveness, this issue is not clearly settled.

Nevertheless, a strong inference remains that race and ethnicity play a role in both the genotype and phenotype as they relate to the epidemiology of hypogonadism.

In summary, the reported prevalence of low T in older men range from 5.6% to 50%, depending upon study design, level of T blood concentration used, and study subjects' age. Combining serum T measurement with signs and symptoms most commonly seen with androgen deficiency are recommended in order to confirm the diagnosis of hypogonadism.

Hypogonadism comes with economic burden as well. An analysis of 8538 men, between the ages of 34 and 65, found direct and indirect cost differences associated with hypogonadism[13]. This study examined an administrative database spanning four years and three months. Men with at least two diagnoses for hypogonadism, or, at least one prescription for testosterone therapy with at least one diagnosis for hypogonadism were considered hypogonadal in the analysis. They were matched against those not satisfying either of the two criteria. Those in the hypogonadal group (n = 4269) had direct health care costs, that exceeded the eugonadal group (n = 4269) by an average of $7100 over the course of the observation window. Due to the expense of treatment for HIV/AIDS, those affected individuals were excluded in another analysis to avoid skewing the difference. The difference in direct costs was then $5579, meaning that the hypogonadal group incurred an additional cost of just over $109 per person per month. Indirect costs went up a little more than $30 per person per month. Examples of mean disease- specific costs for hypogonadal *vs* eugonadal were as follows (these numbers do not exclude those with HIV/AIDS): Cardiovascular and metabolic health: $1453 *vs* $757; Pain: $980 *vs* $365; Mental health: $558 *vs* $176. The hypogonadal group had a higher Charlson's Co-morbidity Index at baseline, with a mean of 0.95, as compared to the eugonadal group at 0.28. In risk-adjusted analyses of costs, the difference in health care costs (both direct and indirect) was $4869, or just over $94 per person per month on average.

This investigation plainly demonstrated higher economic burden and presence of co-morbidities for

hypogonadism. Additionally, it highlighted a potentially serious threat to the interpretation of all observational studies in the testosterone replacement therapy (TRT) field-compliance. Over 31% of individuals in the hypogonadal did not receive TRT during the observation period. Similarly, within the hypogonadal group receiving therapy the proportion of days covered under TRT therapy was only 38% based on medical claims data. These study findings demonstrate that the economic burden for the hypogonadal group is higher than the eugonadal group even when 2/3 of the hypogonadal group did receive the TRT. However, because at least 31% of the hypogonadal group did not receive testosterone replacement, and those that did receive testosterone replacement were covered less than 40% of the time, it's not possible to infer whether or not TRT was mitigating the additional burden. The socioeconomic burden of hypogonadism should be addressed in detail in future observational and clinical trials, to provide robust metrics on the risks, benefits, and costs of TRT.

TRT

An increased awareness of the health risks associated with untreated hypogonadism has caused a substantial increase in TRT utilization in men[14]. The efficacy of TRT has been demonstrated in several randomized clinical trials[15-17] and has shown minor to moderate improvements in lean mass and muscle strength[18,19], increased bone mineral density (BMD)[18,20], modest enhancement in sexual function[21-23], reduced adiposity[18] and lessening of depressive symptoms[24]. In 2011, the estimated sales for TRT were 1.6 billion dollars in the United States[25]. However, significant questions remain regarding the safety of TRT because no large-scale randomized clinical trials have directly compared the health risks of untreated hypogonadism *vs* long-term TRT use[25].

Enthusiasm for TRT utilization has been tempered by concerns regarding the health risks of this therapy. Meta-analyses of clinical TRT trials as of 2010 have identified three major adverse events resulting from TRT: (1) polycythemia; (2) an increase in prostate-related events; and (3) and a slight reduction in serum high-density lipoprotein (HDL) cholesterol[26-28]. Clinical concern over the health risks of TRT was heightened in mid-2013 when a meta-analysis reported increased cardiovascular (CV) risk in men receiving TRT[29]. Similarly, a recent retrospective study reported increased risk of stroke, myocardial infarction, and all-cause mortality in hypogonadal men receiving TRT after angiography[30].

CARDIOVASCULAR AND CEREBROVASCULAR RISKS OF TRT

Two widely established health risks associated with TRT are polycythemia (> 3.5-fold increase in risk)[26,27] and reduced HDL cholesterol[27]. These risk factors represent increased risk for CV and cerebrovascular events. Serious concern regarding the safety of TRT was raised in 2010 when the data and safety monitoring board (DSMB) of a double-blind randomized clinical trial recommended discontinuation of the trial because elderly hypogonadal men (with a high prevalence of chronic disease) experienced an increased incidence of CV events after receiving TRT[31]. This randomized clinical trial was discontinued because 23 participants in the TRT group (approximately 22% of all TRT participants) *vs* 5 participants in the placebo group (approximately 5% of all placebo participants) experienced adverse CV-related events within the first 6 mo. Adverse events ranged from chest pain (n = 1) to myocardial infarction (MI) (n = 3 with one death suspected from MI), with peripheral edema being the most commonly reported side-effect (n = 5).

A large meta-analysis evaluating CV risks associated with TRT (including 27 RCTs and 2994 older men) also reported that TRT increased risk for CV-related events by 1.54 times (odds ratio = 1.54) in comparison to placebo treatment[29]. In a similar but more recent and larger meta-analysis of 75 RCTs on CV risks and TRT, no significant association between CV events (both single and composite events) and TRT was established[32]. However a retrospective study reported that men receiving TRT after angiography (n = 1223) experienced a 29% greater hazard ratio-adjusted rate of MI, stroke, and all-cause mortality (95%CI: 1.04-1.58) at 3 years post angiography *vs* men with untreated hypogonadism (n = 7486)[30]. Finkle *et al*[33] evaluated 55000 patients and reported a more than 2-fold greater risk of MI in men who had received a TRT prescription. These results differ from several smaller analyses reporting heightened CV risk and all-cause mortality in men with untreated hypogonadism[26,28]. This is especially important given that the TRT literature has thus far been equivocal and/or underpowered, despite large, coordinated efforts such as the forthcoming series of trials from Snyder *et al*[34].

As a response to the above study reports, the United States Food and Drug Administration (FDA)[35] the Endocrine Society[36] and the United States Veteran's Administration[37] have called for monitoring and reassessing the health risks associated with TRT, respectively. Since these advisory announcements, a number of literature reports have critiqued the TRT literature, particularly the studies by Vigen and Finkle, for issues associated with the study design, statistical methods, and interpretation of findings[38-40].

Notwithstanding several letters to the editor, and several recent TRT articles showing no increased cardiovascular risk, the United States FDA Joint Advisory Panel voted to change the labeling on testosterone replacement medication until larger studies demonstrate a clinical benefit and account for patient safety[41].

PROSTATE RELATED RISKS OF TRT

Another well-established health risk of TRT is increased incidence of prostate/lower urinary tract-related events (*i.e.*, combined incidence of prostate-biopsy, prostate enlargement, elevated PSA, and prostate cancer)[26]. Several coauthors of this commentary recently conducted a double-blind randomized clinical trial (NCT00475501) and observed that TRT produced a 40% prostate enlargement in older hypogonadal male Veterans over 12 mo[42]. These increased prostate-related risks have raised concern that TRT may increase prostate cancer risk or hasten the development of undiagnosed prostate cancer.

However, no published analysis has reported measurable increases in prostate cancer risk or Gleason score in men undergoing TRT, or in hypogonadal men with a history of prostate cancer undergoing TRT[26,27,43]. Despite this, Calof *et al*[26] estimated that an evaluation of 85862 participants is necessary to detect a hypothetical 20% increase in prostate cancer resulting from TRT. The largest meta-analysis evaluating prostate cancer risk associated with TRT included only 1700 men (*i.e.*, < 2% of the necessary population size)[43].

OTHER PUTATIVE HEALTH RISKS ASSOCIATED WITH TRT

A number of putative health risks have been reported with TRT, including fluid retention[31], gynecomastia[44], liver disorders, and worsening of sleep apnea[45]. These adverse outcomes are worrisome because they represent risks for several serious life-threatening adverse events and for other potentially serious clinical conditions. However, current meta-analyses have not established a definite relationship between TRT and these potential health risks, likely because they lack the statistical power. Additionally, the mechanisms through which T incites the above mentioned health risks are not completely understood, but may result in part from tissue-specific 5α-reduction of T to dihydrotestosterone (DHT)[46] or from the aromatization of T to estradiol. This is especially true in the prostate which highly expresses the type Ⅱ 5α-reductase enzyme. Inhibition of this enzyme via finasteride (a type Ⅱ 5α-reductase inhibitor) or dutasteride (a dual type Ⅰ and Ⅱ 5α-reductase inhibitor) reduces circulating DHT 50%-75% and > 90%, respectively[47], and reduces prostate mass[48] and prostate cancer risk[49]. Our team[42] and others[15] have demonstrated that finasteride also prevents prostate enlargement resulting from high-dose TRT without inhibiting the beneficial musculoskeletal or lipolytic effects of T, indicating the clinical viability of this combination pharmacologic therapy. It is unknown whether other potentially life-threatening health risks and other adverse events discussed above are mediated by the 5α-reduction or aromatization of T.

ALTERNATIVES TO TRT

Given that there is currently no global consensus on the medical approach to testosterone deficiency, it is not surprising that alternative approaches to rectifying low T-levels are great in number, yet also lacking widespread agreement[50]. Several decades of research have been completed evaluating the field of selective estrogen receptor modulators and selective androgen receptor modulators (SARMS). Clomiphene Citrate (CC) is an estrogen receptor modulator that is used in the treatment of male hypogonadism in an off-label capacity. Normally estradiol partially regulates testosterone levels, at the hypothalamus, blunting LH and FSH release from the pituitary. As a selective estrogen receptor modulator, CC interrupts this pathway, and consequently there is a greater stimulation for the production of testosterone in Leydig cells[51].

A cohort of 1150 hypogonadal men were evaluated, and matched to produce a final sample of 93 in three groups: CC, Testosterone Injections (TI), or Testosterone Gel (TG)[52]. Each group consisted of 31 individuals. The research team evaluated changes in serum testosterone and patient satisfaction. All treatment modes were effective at raising T-levels. Changes in T-levels (ng/dL) from pre- treatment to post-treatment were as follows: CC = 247-504, TI = 224-1104, TG = 230-412. Patient satisfaction was equal among groups, though the responses in T-levels were not equivalent. The noted difference was in libido, where injection produced the greatest index of libido on the qADAM questionnaire (4 v. 3 for each comparison of injection v. CC, injection v. TG). CC appears to be a suitable alternative to testosterone supplementation. However, larger randomized clinical trials are needed to determine its proper use, potential safety, and whether this agent effectively mitigates the known side-effects of hypogonadism. Similarly, as reported by Taylor *et al*[51], 104 men received either CC or T-Gel (CC = 65, T-Gel = 39). The CC group had higher post-treatment T-levels, 573 ng/dL v. 553 ng/dL. The monthly cost of T-Gel medication is over three times that of CC (Testim 1%, 5 gm daily = $270/mo, Androgel 1%, 5 gm daily = $265/mo, CC 50 mg every two days = $83/mo). Thus, in terms of cost-effectiveness, CC would appear to be advantageous. However, more research is needed to determine its proper use.

SARMS

The combined research and clinical goals of SARMS are the reductions in catabolic actions initiated by hypogonadism and/or aging in order to preserve skeletal muscle and bone allowing for the individual to maintain functional activities of daily living, reduce fall and fracture risk, and consequent disability. SARMS are of particular interest because of recent guidance documentation[41] on the restriction of exogenous testosterone administration warranted by observational studies indicating an

increased risk of cardiovascular events[30,53]. In light of the recently cited effects on the cardiovascular disease system, SARMS are the most likely candidates to improve skeletal muscle mass in hypogonadal individuals. SARMS are engineered to bind to the androgen receptor without inducing other known side effects (*e.g.*, prostate related events and polycythemia) of TRT. Several SARMS, including JNJ-28330835[54], BMS-564929[55], MK-0773[56], and others have shown a positive levator ani/bulbocavernosus muscle complex/prostate ratio in pre-clinical rodent models, demonstrating an improved anabolic/androgenic ratio is associated with these drugs[57]. The anabolic to androgenic ratio with limited side effects is the therapeutic target of SARMS research.

CONCLUSION

In summary, circulating testosterone concentrations decline throughout the aging process in males[2]. The prevalence of low circulating testosterone (*i.e.*, hypogonadism) is approximately 20% in men between 60-70 years of age and increases to roughly 50% of men over 80 years of age[2]. The use of TRT has increased substantially among men in recent years[14] because of an increased awareness of the risks associated with male hypogonadism (*e.g.*, muscle and bone loss, and increased frailty)[58,59]. However, TRT safety remains of primary concern, as do the potential health risks of untreated hypogonadism. To date, the largest prospective clinical trials that have been conducted on TRT involved only several hundred individuals; as such, they were dramatically underpowered to assess many of the more rare, yet severe health risks that are putatively associated with TRT. Unfortunately, even the largest meta-analyses on adverse events associated with TRT lack sufficient power to detect these and other potentially life-threatening health risks. Additionally, these clinical trials and meta-analyses have only assessed health risks during relatively short-term TRT or for only a very brief follow-up period after the cessation of TRT, which is concerning because once TRT is initiated it is typically continued throughout the lifespan. TRT studies should address additional external factors that may contribute to the reported risks and benefits currently associated with TRT including: diet, exercise, neutraceutical supplementation, sleep, and obesity.

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