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Weighing the Benefits and Drawbacks of Testosterone Replacement Therapy

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SUMMARY

Male hypogonadism—the deficiency of testosterone in the body—is a condition that has sparked increased interest in the discussion surrounding men's health. Many studies have previously explored the use of testosterone replacement therapy to improve the quality of life for patients with this condition. However, further research is required to weigh the long-term benefits and drawbacks of this therapy to determine its safety and efficacy for future patients. This review will highlight the advantages and disadvantages of testosterone replacement therapy in men suffering from hypogonadism. Improvements highlighted in this study include increased libido, muscle mass, and self-esteem. These improvements weigh against potential side effects such as organ cancers and systemic tissue damage. This review will also explore which patients are most suitable for the treatment and how the research surrounding this topic can be improved moving forward. By analyzing a range of short- and long-term studies with empirical data, observational and surveyable evidence, this review will provide insight into the basics of testosterone replacement therapy, the potential benefits and risks associated with its use.

ABSTRACT

Over the last few decades, the discussion surrounding men's health issues has sparked an increased interest in the treatment of male hypogonadism—the deficiency of testosterone in the body—through testosterone replacement therapy to improve patients' quality of life. A worthwhile consideration for further research a is to explore the long-term benefits and drawbacks that may testosterone replacement therapy prescription to patients moving forward. It is worth weighing treatment effects, as well as examining which patients are most suitable for the therapy and why, from a health cost-benefit analysis. Many of the benefits that this review will be related to the symptoms of hypogonadism—most notably decreased libido, muscle mass, and emotional well-being. This review will also consider the potential side effects of treatment through short- and long-term studies which include observational, surveyable, and empirical data. Some drawbacks include increased risk of various organ cancers and systemic tissue damage. Holistically, this review will provide insight on the basics of testosterone replacement therapy, who benefits from it the most, who is at risk, and how its understanding can be improved moving forward.

Keywords: Testosterone replacement therapy, hypogonadism, muscle hypertrophy, sexual function

INTRODUCTION

The perception of testosterone replacement therapy (TRT) for aging men is particularly controversial. TRT is a legalized treatment option that alleviates testosterone deficiency symptoms, such as decreased libido, erectile dysfunction, depressed mood, anemia, and loss of muscle and bone mass, by increasing serum testosterone levels to healthy physiological ranges.[1] Late-onset hypogonadism (LOH) has increased nearly 7% in men within the last 40 years according to a retrospective cohort study conducted in China.[2] Most doctors recommend that the first line of treatment should remove the root cause of LOH, such as treating obesity, type 2 diabetes (T2DM) or any metabolic syndrome (MetS).[2] However, many patients simply require the assistance of exogenous testosterone supplementation to reach recommended hormone levels. As TRT prescription rates increase, the treatment option's efficacy and safety are paramount. This systematic review's objective is to analyze the intended benefits as well as adverse effects of TRT for males with subnor-

mal free testosterone levels. This review will evaluate the current literature around TRT to determine its relevance and reliability.

1. METHODS OF TESTOSTERONE ADMINISTRATION

Testosterone can be administered in a multitude of ways into the body to increase serum testosterone levels. Oral testosterone supplements are sold in most recreational health outlets. However, they are considered to be ineffective due to a combination of poor intestinal absorption capacity and rapid hepatic metabolism, rendering them useless biochemicals once in the bloodstream.[3] Buccal testosterone is an uncommon way to improve serum concentrations, involving mucoadhesive tablets applied to the gums of the mouth to provide continuous release directly into the systemic circulation, bypassing the liver and yielding relatively high bioavailability.[4] Nasal testosterone is another uncommon form of deliverance, consisting of a thixotropic gel applied to the nasal cavity, continuously delivering testosterone directly into the circulatory vessels.[5] Next, the subdermal method employs testosterone pellets of a crystalline preparation which are designed and implanted for consistent and prolonged-release.[6] Lastly, intramuscular testosterone injections are commonly used to treat hypogonadal males and female-to-male transgender patients.[7]

2. TYPES OF TESTOSTERONES

Testosterone propionate, cypionate, and enanthate are different forms of testosterone. These forms differ in their esterification, which affects their pharmacokinetics. Essentially, the different compounds will vary in absorption, distribution, metabolism, and excretion by the body. Regarding esterification, propionate has the shortest ester chain, compared to cypionate's long chain and enanthate's even longer chain.[3] The shorter chain allows the compound to enter the bloodstream quicker. The time of action is also a significant factor to consider. Propionate has a shorter half-life than the others. Therefore, propionate is rapidly absorbed and eliminated from the body, which requires the user to take more frequent injections to maintain adequate serum concentrations.[4] The esterification and time of action also factor into the distribution of the compounds in the body. Propionate is rapidly distributed throughout the bloodstream due to its comparative size and pharmacokinetics and is excreted through metabolism at a faster pace as well.[5]

3. BENEFITS OF TRT

Restoring testosterone levels to the normal range using TRT can improve many facets of life for individuals suffering from hypogonadism. Notable and documented benefits of TRT include improved mood, energy, well-being, cognition, sexual function, muscle mass, strength, erythropoiesis, bone mineral density, and cardiovascular health.

3.1 Sexual Desire, Function, and Performance

Frequent erectile dysfunction is a common occurrence for men beyond their pubescent years.[7] This is likely due to the correlation that exists between free testosterone and erectile and orgasmic function.[8] As free testosterone decreases beyond puberty, we can expect sexual activity, functionality, and performance to decrease accordingly because of increasing dysfunction of androgen receptors.[9,10] Long-term follow-up of TRT in hypogonadal males and controls indicated, through self-assessment of the sexual characteristics, significant improvements in the testosterone-treated group only.[11] Indeed, Hajjar et al. (1997) showcased that TRT enhanced libido and frequency of sexual acts and sleep-related erections.[11]

Unfortunately, for some men, TRT alone is not enough to improve sexual performance, leading to a reassessment of the causes of erectile dysfunction. There is evidence by Shabsigh et al. (2004) that taking phosphodiesterase type-5 inhibitors—i.e., sildenafil or Viagra—could have a synergistic effect with TRT for men suffering from this condition.[12] These inhibitors work in the penis and lungs by blocking the breakdown of cyclic guanosine monophosphate (cGMP) which results in prolongation of the mediators of vasodilation, most notably including nitric oxide (NO).[13] Karazindiyanoglu and Cayan (2008) also suggests TRT can improve lower urinary tract symptomatology (LUTS) and overall bladder functionality by increasing capacity.[14] Mitigating these symptoms has shown to improve cases of erectile dysfunction in patients.[15]

3.2 Bone Mineral Density

Osteopenia, osteoporosis, and fracture prevalence rates are significantly greater in hypogonadal men, regardless of age, as suggested by Meier et al. (2008).[16] Testosterone supplementation has been shown to improve bone mass by increasing osteoblastic activity, and through aromatization to oestrogen, reducing osteoclastic activity.[17] Osteoblasts are responsible for new bone formation, while osteoclasts are responsible for aged bone resorption.[18,19] Morley et al. (1993) found that osteocalcin levels, indicative of osteoblast activity, were elevated, whereas hydroxyproline excre-

tion, indicative of bone resorption, were decreased.[20] At normal physiological conditions, formation and resorption rates are stable. However, when the balance is disturbed, as in the case of hypogonadism, bone architecture and function will be abnormal. TRT can aid in the return normal homeostatic conditions.

3.3 Muscle Mass and Strength, and Fat Mass

Unfortunately, for ageing men, body composition has shown to change in negative ways. Indeed, muscle tissue tends to decrease, and redistributed fat mass increases.[21] Decreases in overall muscle mass and strength can limit functionality and increase injury risk, and deter overall quality of life, especially for those who lead active lifestyles, habitually or professionally. Differently, increased fat mass can lead to morbidity through increased cardiovascular and immune system stress. However, the declining testosterone levels are a contributing factor to these negative changes, but not entirely culpable. Furthermore, Mauras et al. (1998) suggested that human growth hormone (HGH) decreases with age because of somatopause.[22] HGH binds to hepatic receptors and stimulates the expression and release of IGF-1.[23] IGF-1 then stimulates testosterone production by testicular interstitial cells to enhance steroidogenesis.[24] This results in increased muscle protein synthesis and growth.

Given this information about the testosterone production cascade, one would reasonably consider supplementing growth hormone to treat the testosterone deficiency directly, however, this is inadvisable. HGH is not an effective treatment for low testosterone. While it impacts overall body composition, the safety and validity of this treatment option is not sufficiently grounded. As suggested by Birzniece et al. (2011), HGH vs TRT had no statistically significant difference in serum free testosterone concentration.[25] However, growth hormone is a more broadly utilized drug compared to testosterone, which can lead to many unintended physiological effects if the goal is simply to treat hypogonadic symptoms. Hence, supplementing with TRT is the safest and most efficient means to improve muscle mass and strength.

Testosterone can also decrease fat mass by inhibiting the expression of lipogenic genes in fat cells resulting in global lipid oxidation.[26,27] While the underlying mechanisms aren't entirely understood, some researchers suggest that certain genes within the fat cells are inhibited by testosterone and reactivated through its aromatization into oestrogen.[28] Miller et al. (2016) supported this hypothesis, suggesting that oestrogen levels can modulate hepatic lipogenesis.[29] This is a common issue in men who take anabolic steroids, most famously represented through gynecomastia—fat accumulation in breast tissue from increased testosterone aromatization into oestrogen.[30] Hence, aromatase inhibitors are recommended to be taken in conjunction with TRT to mitigate this unnecessary fat accumulation, while still reaping the benefits outlined thus far.[31]

3.4 Mood, Energy, and Quality of Life

Several studies have correlated low serum testosterone levels with lower quality of life.[32] The attributes measured included low libido, dysphoria, fatigue, and irritability—all of which correspond to major depressive disorders.[33] Schmidt et al. (2004) found that the depressive symptoms of hypogonadal patients were significantly reduced, if not entirely reversed, by TRT.[34] However, it is important to be critical of this evidence as contrary results have also been published. Specifically, a study by Tricker et al. (1996) found that TRT administration had no significant effect on depressed hypogonadal men, relative to their nondepressed test subjects.[35] This begs the question of whether TRT should be prescribed to men who suffer from depressive symptoms, which are likely the result of serum testosterone deficiencies.

For this, we will have to compare the effects of depression treatment and TRT. Ehrenreich et al. (1999) suggested that testosterone may serve as an effective antidepressant, given that their study explored a large sample of men with depressive symptoms and found that testosterone gel significantly improved depressive symptoms in groups that did not receive placebos nor selective serotonin reuptake inhibitors (SSRIs). It is important to note that a possible limitation of this data is that there was no follow-up study several weeks beyond the trial treatment period, limiting its long-term applicability. Indeed, further trials should be conducted to thoroughly explore this topic as the evidence proposed thus far has been conflicting to say the least. Nonetheless, if mental health is an issue for someone suffering from hypogonadism, TRT is worth considering because as the benefits previously outlined, it clearly suggests that it can improve physical health and has limited negative side effects on mental health.

3.5 Cognition

Gillett et al. (2003) have demonstrated through clinical research that androgen deficiency may enhance the expression of peptides involved in Alzheimer's disease, including beta-amyloid.[36,37] Indeed, decreases in serum testosterone may be responsible for visual and verbal memory declines as men with equivalent ratios of sex-hormone binding globulin with serum testosterone have higher incidences of dementias.[38]

Spatial abilities and mathematical reasoning are components of verbal and visual memory that may be impacted. Gouchie and Kimura (1991) found that a

strong relationship exists between men's testosterone levels and their memory and cognitive capacity, even after it was adjusted for age and education as confounding variables.[39] Lu et al. (2006) found patients suffering from Alzheimer's disease experienced significant improvements in cognition and mood following TRT.[40] However, there is some contradictory evidence in this discussion as Maki et al. (2007) found that TRT accelerated working memory declination and brain impedance.[41] Finally, Tan and Culberson (2003) found that there was no significant difference in cognitive capacity and function following TRT in androgen-deficient men, suggesting that this area is prudent for further investigation before one considers TRT if they are at risk for dementia-related diseases.[42]

With TRT being a relatively novel therapy, only becoming popularised in the early 1990s and 2000s, the rise in concern over potential adverse effects is significant. Due to the lack of factual data surrounding the relationship between TRT and adverse health effects, this review will delve deep into the literature to find any causational or correlational evidence of the treatment's medical safety.

4. DRAWBACKS OF TRT

4.1 Liver Dysfunction

The causal relationship between TRT and hyperandrogenism with liver function is certainly understudied. Numerous concerns associated with TRT has found in the liver including hepatic tumours, cholestasis, hepatotoxicity, peliosis, hepatitis, hepatocellular adenoma, and total failure. These deleterious effects do not seem to be associated with transdermal or intramuscular injection; therefore, it is recommended that oral forms of TRT are not administered.[43]

However, a general lack of testosterone or LOH has been known to predict even worse outcomes, such as Hepatitis B and total liver failure.[44] Moreover, Westaby et al. (1977) found that a low testosterone serum (<142.39 ng/dL) is independently associated with severe outcomes of HBV-related acute-onset liver failure.

4.2 Prostate Dysfunction and Cancer

With the use of TRT becoming more common, the correlation between its use and incidents of prostate dysfunction and cancer is becoming more prominent. Fowler and Whitemore (1982) reported that exogenous testosterone given to metastasized prostate cancer patients resulted in increased advancement of malignant cells.[45] One longitudinal study found a signification between the relationship between men diagnosed with prostate cancer and endogenous testosterone supplementation.[46] However, a 3-year meta-analysis composed of 18 prospective studies with 3,500 men investigated the correlation between prostate cancer and TRT and found no association between serum androgen levels and the risk of prostate cancer.[47]

Concerning premalignancy and prostatic intraepithelial neoplasia (PIN) are risk factors for developing prostate cancer.[47] However, there is a lack of long-term data on the use of TRT in men with PIN.

Nevertheless, there have been reports of metastatic prostate cancer in older men on testosterone therapy. Due to this potential, risk practitioners and doctors are reluctant to administer testosterone to those who may be at risk of PIN.[47] Therefore, men being administered with TRT should have frequent monitoring within the first 3-6 months.

4.3 Elevated Red Blood Cell Count

Strong evidence suggests that increased testosterone levels, regardless of way-of-entry, stimulates erythropoiesis: production of red blood cells.[48] This can progress to polycythaemia: abnormal levels of red blood cells in the blood. While polycythaemia doesn't have a statistically significant correlation with TRT, it is an accepted side effect of. Considering this information, TRT is often a suggested remedy for men who suffer from anemia—low red blood cell count—due to its erythropoietic properties.

Increasing haematocrit—red blood cell count—past the regular male concentration of 4.0-5.9 x 10*12/L can have adverse side effects, ranging from increased blood pressure from thickening of blood to blurry vision and headaches. Polycythaemia may have an increased incidence of vascular events, including but limited to, stroke, myocardial infarction, or deep vein thrombosis. Therefore, it is highly suggested that while on TRT, individuals should not only monitor their complete blood count (CBC) but have their baseline CBC measured prior to the start of their treatment plan.

4.4 Compromised Immune System

For unknown reasons, men have always been more susceptible to bacterial, fungal, and parasitic infections than women.[49] In a retrospective explorative analysis conducted by Lanser et al. (2021), testosterone levels measured through PCR confirmed SARS-CoV-2 infection.[50] Interestingly, they recorded that lower testosterone levels were linked with a more advanced immune activation. This was further supported by the aforementioned comment on women's better immune systems, while they possess lower levels of testosterone than men.[50]

A Stanford lead study looked to prove a relationship between higher levels of serum testosterone with a

lowered immune response. They were unable to find any indication that testosterone actively suppresses the immune system in any direct way. However, the researchers noticed a peculiar interaction where testosterone was able to dampen the immune response, but additional research was suggested before drawing any conclusions between TRT and a reduced immune response.[49]

The sperm production hypothesis offered an alternative hypothesis that the immunosuppressive effect of testosterone protects haploid spermatozoa. Hillgarth et al (1997) suggested testosterone suppresses antibody protection within the blood-testis barrier.[51] However, this theory fails to explain the change in the numbers of circulating leukocytes associated with elevated testosterone.

However, the question remains about why testosterone, a hormone designed to increase libido, bone density, and lean muscle mass, dampens the immunity of the organism. These are questions to consider with one's clinician if they are considering TRT, especially individuals who suffer from autoimmune or chronic illnesses. Nevertheless, the inherent properties of TRT to objectively increase serum testosterone raises concern for those considering administering it.

4.5 Damaged Cardiovascular System

The relationship between TRT and cardiovascular outcomes is conflictive to say the least. Hypogonadism is an increasingly diagnosed disorder in age, overlapping with increasing risk of cardiovascular events.[52] Patients with established cardiovascular disorders considering TRT should heavily weigh the benefits, drawbacks, and possible side effects, as TRT can have variable responses on different individuals. TRT has been depicted as having cardio-protective, vasodilatory, and anti-inflammatory properties, but in some instances, it can be vasoconstrictive, pro-atherosclerotic.[52]

To shed some light on this conundrum, Michos et al. (2022) completed a meta-analysis on 35 placebo-controlled trials of TRT that included 5,601 men with low baseline testosterone concentrations.[53] During the short follow-up, there was no increase in cardiovascular events between the TRT group and the placebo group (odds ratio 1.07). The authors did witness an increase in cholesterol, but this change was statistically insignificant.

Relating to red blood cell count, those who undergo any form of testosterone therapy will undergo stimulation of erythropoietin. This will evidently increase red blood cell count, which in some circumstances can have a sharply increased risk of high blood pressure (hypertension).[54] According to Dalmasso et al. (2017), men who used synthetic derivatives of testosterone have a higher risk of ventricular remodelling and sudden cardiac death, but there was no direct correlation to TRT.[54] Hence, further investigation is required to elucidate the relationship between TRT and cardiovascular outcomes.

5. WEIGHING THE BENEFITS AND DRAWBACKS OF TRT

To adequately weigh the benefits and drawbacks of TRT, future patients are recommended to explore contraindications with their healthcare provider to ensure that the treatment is a safe and viable option. This will include looking at all the possible risks associated with TRT and properly evaluate if the safety risk is minimized during the treatment period. This will vary significantly between individuals as some men need a few weeks to 'jumpstart' their endogenous production through TRT, while others become entirely dependent on exogenous dosages to sustain their serum testosterone levels for life.

Infections at the site of intramuscular injection are not uncommon for patients undergoing TRT as properly cleaning the site can be challenging. This is because the patients are likely not given sufficient training and literature on how to minimize infection risk, during injection, by their physician. Additionally, most injection sites are at the glutes, which are hard to reach and see for most individuals. These instances of infections are easily treated with antibiotics, and a proper consultation with an attending physician can improve the future treatment, but the risk should be noted regardless.[55]

Prostatic carcinoma is a strong opponent for anyone considering TRT. This applies to any males who are genetically at risk for or have previously been diagnosed with prostate cancer. It has been suggested by Huggins and Hodges (1941) that prostate cancer is androgen-dependent, so taking exogenous testosterone to raise serum concentrations may put oneself at risk for the disease.[56] There is no clear evidence of a causational relationship. A collaborative analysis by Roddam et al. (2008) demonstrated that the men with the highest risk of prostate cancer had the lowest serum testosterone levels.[57] Conversely, Mohr et al. (2001) found no correlation between the two variables.[58] Regardless, it is likely not wise to administer TRT as it may exacerbate the likelihood to acquire prostate cancer, especially if there is concern from family history or previous cancer incidents.

Erythrocytosis is another consideration for physicians and patients deliberating TRT. As previously mentioned, TRT can significantly elevate hematocrit.[59] Consulting a physician on one's hematocrit before discussing TRT options is crucial because a higher red

blood cell count than a normal can be extremely problematic throughout and after treatment. Erythrocytosis can cause symptoms of hyperviscosity, such as headaches, fatigue, blurred vision, and paresthesias.[59] Additionally, elevated erythrocytosis can lead to secondary effects. For instance, congenitally, the body will have a high oxygen affinity Hb and altered intracellular oxygen sensing, coupled with EPO receptor upregulation.[60] This will lead to hypoxic states. Systemically, lung disease, shunt, and hypoventilation are expected; locally, renal artery stenosis and ESRD are exected.[60]

Congestive heart failure (CHF) is a growing health problem around the world, especially among aging men. Despite modern medicine, advancement concerning the detection, diagnosis, and treatment of CHF is bleak. However, TRT has been discussed significantly in the scientific literature as being a viable supplement to regular practice in correctly treating and managing CHF. While the physiopathological mechanism and effectiveness of TRT concerning the cardiovascular system is unclear, some evidence has emerged that TRT could improve muscle strength, exercise tolerance, functional pulmonary capacity, insulin sensitivity, and adjust the neuroendocrine factors in patients with CHF.[61] A collection of studies revealed that TRT could significantly improve the exercise capacity of patients, measuring factors such as 6MWD (6 -min walk distance) and SWD (shuttle walk distance), as suggested by Malkin et al. (2006).[62] Mirdamadi et al. (2014) replicated this same study and found similar results.[63] A similar study conducted by Caminit et al. (2009) found that TRT groups improved their exercise capacity, but the study explored more details beyond just that.[64] They found that there was a tendency toward blood pressure decrease, possibly suggesting that this treatment option be considered more favourably for patients with CHF. In CHF, most patients suffer a gradual decline in muscle mass, strength, and endurance, which is reflected in the maladaptive imbalance and relative deficiency of anabolic hormones, mainly testosterone. A testosterone deficit leads to the metabolic shift favouring catabolism, a major underlying mechanism for tissue wasting seen in CHF. Whether that testosterone deficiency is a precursor to the development of CHF, a consequence of the condition, or a combination of both is unclear at this time.[61] However, testosterone supplementation in patients with CHF is associated with an improvement in exercise capacity and muscle strength which will be beneficial in improving quality of life, clinical events, and safety.

CONCLUSION

As men age into their 30s, 40s, and 50s, peak testosterone steadily declines, with the most rapid decline occurring around the mid-50s.[1] However, the advancements of TRT have provided a remedy to this issue for middle-aged men. TRT is proven effective in reducing the effects of testosterone deficiency discussed above.[3] While research outlining the benefits of TRT are plentiful, those highlighting its connection to various pathologies and morbidities are certainly lacking.

Certain pathologies relating to the immune system and cardiovascular systems have some underlying concerns, but not enough definitive data is available to make any clear-cut recommendations. However, the underlying concern should be sufficient in encouraging caution and extreme monitoring when administering TRT.

Male hypogonadism and its treatment are a rapidly evolving area. The benefits and risks of testosterone therapy must be discussed with the patient. An assessment of risk factors previously outlined in this literature review should be explored thoroughly before deciding if TRT is a viable option for the patient. There are benefits to TRT, such as improvements in muscle mass and strength, fat mass, sexual function, and general well-being. However, it is illogical to ignore the plethora of negative impacts that can arise in certain individuals if they were to engage with exogenous testosterone supplementation. Patients and physicians should be cognizant of their knowledge gaps as well; the academic literature surrounding many of the risk factors is unexplored or in their novel stages of discovery. Studies conducted to date have been too small to address long-term potential adverse effects and there are risks in extrapolating benefits from epidemiological studies. Larger clinical trials coupled with meta-analyses of the extensive short-term data and limited long-term data will benefit many physicians and patients in exploring the long-term benefits and risks of TRT. Patients will have to carefully weigh their options with their medical advisor, so they are tending to their underlying conditions safely and effectively. If treatment is considered, there should be constant monitoring of symptoms and signs of improvement. If not observed, then treatment should be discontinued, and the patient will be investigated for other possible diagnoses.

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