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TESTOSTERONE REPLACEMENT THERAPY: ASSESSMENT OF CARDIOVASCULAR RISKS

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Abstract: Objective: Analyze the results of updated 2023 studies to evaluate cardiovascular risks related to testosterone replacement therapy in men, aiming to provide a basis for clinical recommendations. **Methodology**: Narrative bibliographic review using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The following search terms were used, along with the Boolean operators "AND" and "OR": Testosterone Replacement Therapy AND Cardiovascular Risk. After applying the inclusion and exclusion criteria, 15 articles were selected for extensive analysis. **Review**: The results reveal a broad-spectrum view of the topic in question, with the impact of testosterone replacement on the cardiovascular system not being completely evident. In addition to the clinical and physiological benefits of testosterone replacement therapy (TRT), some studies point to a possible increase in cardiovascular adverse events, such as venous thromboembolism, cardiovascular morbidity and mortality, with intramuscular administration being more harmful in this regard, especially in obese men., elderly people, patients with type 2 diabetes, metabolic syndrome and a history of previous cardiovascular disease. Furthermore, there was a tendency to regularly monitor patients on TRT, especially hematocrit levels, to avoid complications such as venous thromboembolism. **Final Considerations**: The need for clinical and laboratory monitoring of patients is evident, especially in at-risk populations, such as the individualization of therapeutic choice. However, the assessment of the cardiovascular risks associated with TRT in men is still in its infancy due to the limitations of clinical tests, and future studies are needed to better understand the cardiovascular risks of hormone replacement in the target population.
Keywords: Testosterone replacement therapy; Cardiovascular disease; Cardiovascular risk.

INTRODUCTION

Testosterone replacement therapy (TRT) is indicated in the treatment of primary and secondary symptomatic hypogonadism. Testosterone is the main male androgenic hormone, with essential physiological functions for the male reproductive system and in the maintenance of sexual characteristics throughout life, being secreted by Leydig cells in the testicles and regulated by the Hypothalamus-Pituitary-Gonadal (HHG) axis (Jhawar and Chirila, 2023). Testosterone levels peak around the age of 30, declining at a rate of approximately 1-2% per year with advancing age. Hypogonadism occurs when there is testicular failure (primary hypogonadism), due to disturbances in the hypothalamus or pituitary gland (secondary hypogonadism) or when they occur concomitantly (mixed hypogonadism), with the main clinical manifestations being erectile dysfunction, reduced libido, anemia, osteoporosis, sarcopenia and gynecomastia. Diagnosis requires two morning testosterone samples below 270 ng/dL (reference: 270-1070 ng/dL), with the recognition of androgen deficiency and appropriate tests being extremely important for a correct diagnosis (Ahmed et al., 2020).

According to guidelines published by the American Association of Clinical Endocrinology, when diagnosing hypogonadism in symptomatic male patients with low serum levels of total testosterone, TRT must be considered, as there is evidence regarding testosterone supplementation in androgen deficiency, indicating benefits. in improving symptoms and maintaining normal levels of the hormone in question. TRT has benefits on erectile function, libido and other sexual functions in men with hypogonadism (total T < 12 nM), as indicated by randomized clinical trials and observational studies (Haddad et al., 2007).

Studies report benefits, such as improved symptoms in cases of androgen deficiency, but suggest small harmful effects of long-term use of this hormone on cholesterol, blood pressure and glycemic control. Thus, due to the fact that existing studies do not present satisfactory and conclusive evidence, there are concerns about its potential cardiovascular effects (Haddad et al., 2007). However, studies have shown conflicting and inconclusive evidence regarding cardiovascular effects and risks in patients on TRT, and to date there are no clinical trials that demonstrate robust data in investigating the potential association between testosterone therapy and cardiovascular risks. As mentioned above, with senescence, testosterone levels tend to decrease and the burden of chronic diseases, along with cardiovascular risk, increases, making it difficult to establish a true causal relationship in the increase in cardiovascular events in patients on TRT (Jhawar and Chirila, 2023).

The inconclusive evidence on potential cardiovascular risks related to TRT is largely due to the scarcity of rigorous and well-structured clinical trials, as many of the existing studies are retrospective and have limitations such as unrepresentative study populations, periods of limited follow-up, confounding uncontrolled variables and small sample sizes, compromising the generalization and interpretation of data. Another recurring disadvantage in clinical trials is the heterogeneity in the testosterone formulations used, which may serve as an additional confounding factor that may influence discrepancies in observed results. This scenario is complicated by the presence of potential confounding factors, such as diabetes, obesity, sleep apnea, human immunodeficiency virus (HIV) infection, chronic kidney disease and chronic obstructive pulmonary disease (Ahmed et al., 2020).

Off-label prescription of TRT is frequent, even in the face of limited evidence, which highlights the need for more studies to clarify the relationship between TRT and cardiovascular risks. This is because, although there is evidence of improvements in cardiovascular risk factors with TRT in men with late-onset andropause (HA), it is essential to approach this therapy with caution, taking into consideration, adequate patient selection and monitoring of blood levels. testosterone and cardiovascular risk factors (Khera; Miner; Jaffe; Pastuszak, 2021).

Given the context highlighted, there is a need to analyze recent studies, which allow the possible cardiovascular risks associated with TRT to be assessed with greater precision, providing crucial information to guide clinical decisions and treatment recommendations, with the aim of improving safety. and effectiveness of therapy, directly reducing the risks to the cardiovascular health of male patients. Considering the uncertainties and gaps in existing evidence, the aim of this review is to evaluate the cardiovascular risks related to testosterone replacement therapy in men, aiming to provide a solid basis for clinical recommendations for such an approach.

METHODOLOGY

The Rbibliographical review developed according to the criteria of the PVO strategy, which represents: Population or Research Problem, Variables and Outcome. The research was guided by the following search question: "What are the cardiovascular risks associated with testosterone replacement therapy in men, according to the updated 2023 studies?" The searches were conducted in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The following search terms were used, combined with the Boolean terms "AND" It is "OR": Testosterone Replacement Therapy AND Cardiovascular Risk. From this search, we initially identified116articles, which were submitted to the selection criteria.

The inclusion criteria were: articles in English; published in the period 2023 and 2024; that addressed the themes proposed for this research; studies such as systematic reviews and meta-analysis of randomized clinical trials, available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, we selected15articles to compose the collection of this study.

REVISION

The discussion on the indications, benefits and risks of testosterone replacement, with an emphasis on cardiovascular risks, reveals a multifaceted view of this treatment. According to the analysis of current literature, the impact of testosterone replacement on the cardiovascular system is still uncertain. Since the change made by the FDA in March 2015 regarding the possible cardiovascular risks associated and many studies have attempted to analyze the adverse effects of this therapy, but without much success due to the high rate of methodological errors (Blackwell; Blackwell; Blackwell, 2023).

Regardless of the debate on the topic, it is agreed among the articles analyzed that the recommendations for the use of hormone replacement with testosterone are clear. According to Ahmed et al. (2020), TRT must be performed for all men with symptomatic hypogonadism as soon as the diagnosis is confirmed. Such treatment is related to improving erectile function, libido and other aspects of a man's sexual life (Corona; Torres; Maggi, 2020; Khera; Miner; Jaffe; Pastuszak, 2021). Furthermore, serum testosterone

levels are inversely related to the number of comorbidities, such as type 2 diabetes (Corona; Torres; Maggi, 2020), and also inversely related to the mortality rate from cardiovascular diseases (Khera; Miner; Jaffe; Pastuszak, 2021; Gencer et al., 2021).

In addition to improving the quality of sexual life and reducing the risk of comorbidities, TRT has also proven useful in improving physiological capacity. TRT has proven useful for increasing muscle mass in obese patients, improving the state of sedentary lifestyle (Corona; Torres; Maggi, 2020), reducing the amount of fat mass and visceral fat (Khera; Miner; Jaffe; Pastuszak, 2021; Blackwell; Blackwell, 2023), improvement in metabolic syndrome (Blackwell; Blackwell; Blackwell, 2023) and improvement in aerobic capacity and mood (Gagliano-Jucá and Basaria, 2019). However, some articles, such as those published by Gagliano-Jucá and Basaria (2019), Kharaba et al. (2020) and Khera, Miner, Jaffe and Pastuszak (2021), still question the effects of exogenous testosterone on vitality and physical performance.

A current trend is identified regarding the management, monitoring and follow-up of patients using TRT, as well as male populations that are at greater risk. About treatment: testosterone replacement therapy is indicated as therapy for hypogonadism, even in patients with a certain known cardiovascular risk. For monitoring, physical examination with attention to signs of hypogonadism, as well as laboratory tests and bone physiology investigation tests (densitometry, serum calcium levels and parathormone levels) were mentioned. Based on the studies included in this review, it was found that the male populations most at risk are: obese, elderly, patients with type 2 diabetes mellitus, patients with metabolic syndrome and patients with a history of previous cardiovascular disease (Kanakis et al., 2023).

Reduced testosterone levels may contribute to fat accumulation and insulin resistance, indicating a possible dual relationship between obesity and testosterone deficiency (Kanakis et al., 2023). Within this scope, the study demonstrated evolution in body composition (fat reduction and increase in lean mass) in obese men (BMI equal to or greater than 30 kg/m^2), with recurrent low testosterone concentration (<12 nM) and a hypocaloric diet.

However, there was no change in body weight compared to placebo, which can be justified by a meta-analysis with similar results, which found an inverse and equivalent variation in lean and fat mass. Available evidence establishes that lifestyle modifications are a priority for both improving physical structure and increasing testosterone levels in obese individuals. However, the increase in testosterone after this type of approach is modest - around 2 nmol/L - (Corona; Torres; Maggi, 2020). Likewise, participation in lifestyle change programs can be inconsistent, with effectiveness inversely proportional to time, and insufficient results to generate significant clinical benefits - generally 2 to 4 kg - (Kanakis et al., 2023). Therefore, it is plausible to use short-interval TRT to increase muscle mass and allow obese patients to overcome the state of overeating and inactivity, becoming capable of improving their lifestyle habits. Another option would be the combined use of TRT and supervised feeding, which could have better results. However, the available clinical trials and the sample of patients involved are still insufficient to draw conclusions (Corona; Torres; Maggi, 2020).

Despite the highlighted effects on patients' body composition, the impact of TRT on glycemic, lipid and blood pressure indicators are limited, TRT must not be considered as an alternative treatment for type 2 diabetes

(DM2) or metabolic syndrome (MS), (Corona; Torres; Maggi, 2020). In men with hypogonadism, abrupt discontinuation of TRT may reduce insulin sensitivity. Continuous treatment tends to prevent this reduction. Furthermore, androgen deprivation therapy for prostate cancer increases the risk of developing metabolic syndrome and diabetes, which highlights the complexity of hormonal effects on metabolism (Gagliano-Jucá and Basaria, 2019).

This way, it becomes apparent that testosterone supplementation could be an important factor in maintaining the quality of life of men, especially those with hypogonadism.

However, not everything is favorable. Many studies, such as those by Khera, Miner, Jaffe and Pastuszak (2021), indicate that the positive effects only appear within a physiological concentration range, which is approximately between 300-1,100 ng/dL, and which is often exceeded in some replacement regimens. Furthermore, the time and route of administration also influence the outcome of the treatment. According to the same study, the greatest risk for adverse events resulting from replacement occurs in the first 2 years of treatment. It has also been proposed that the route of administration could be a predisposing factor for adverse cardiovascular effects, with intramuscular administration being the most harmful (Gagliano-Jucá and Basaria, 2019).

Some studies have shown that testosterone replacement therapy was associated with a greater risk of venous thromboembolism, cardiovascular morbidity and mortality, due to factors such as an increase in hematocrit, which leads to greater blood viscosity, and an increase in thromboxane A2 concentrations, which results in increased platelet aggregation (Gencer et al., 2021; Kharaba et al., 2020; Corona; Towers; Maggi, 2020; Cannarella et al., 2024). Furthermore, studies suggest that TRT can increase hematocrit through direct action, resulting in an increase in erythrocyte production in the bone marrow, and indirectly, through the induction of erythropoietin and inhibition of hepcidin (Corona; Torres; Maggi, 2020).

Testosterone-induced erythrocytosis is influenced by both the dose and its serum level, therefore higher doses and levels may be associated with a greater risk of developing complications caused by erythrocytosis and blood hyperviscosity (Khera; Miner; Jaffe; Pastuszak, 2021).

Furthermore, studies state that an increase in cardiovascular events, such as stroke or acute myocardial infarction, was found in men who received testosterone replacement therapy (Gagliano-Jucá and Basaria, 2019), which may link them to a shorter duration of treatment, reaching the peak of cardiovascular risk in the first 3 months of replacement, and progressively decreasing thereafter (Khera; Miner; Jaffe; Pastuszak, 2021).

On the other hand, some studies have reported beneficial changes in the ECG, such as improvement in ST segment depression time in exercise tests (Gagliano-Jucá; Basaria,2019), and decreased QT interval in the elderly, without interfering with their heart rate, which can be considered a cardioprotective effect due to the higher prevalence of tachyarrhythmias and mortality in patients with long QT (Kharaba et al., 2020). Furthermore, testosterone treatment had an effect cardiac positive ionotropic effect, due to the rapid relaxation of cardiomyocytes after intense hypercontractility (Kharaba et al., 2020).

According to Blackwell, Blackwell and Blackwell (2023), testosterone has been linked to cardioprotective, anti-inflammatory and vasodilatory factors, but it has also been associated with thrombogenic, inflammatory and vasoconstrictive properties.

Therefore, due to the disagreement in the studies analyzed, the American Urological Association stated that the influence of testosterone replacement treatment on the risk of cardiovascular events cannot yet be determined, requiring further studies on the topic (Khera; Miner; Jaffe; Pastuszak, 2021). However, the FDA concluded that there is insufficient evidence to prove that TRT is leash any cardiovascular risk, and therefore, there would be no reason to prohibit it for any group of individuals (Ahmed et al., 2020).

For Loo et al. (2019), the increased risk of cardiovascular (CV) and cerebrovascular events was mainly attributed to a higher incidence among men in the middle-aged age group, while for patients aged 60 - 75 years there was no statistical significance to conclude an increase in risk of CV events. In contrast, two pharmacovigilance studies demonstrated an increased risk of CV events in patients with hypogonadism, one of which, based on an extensive Medicare insurance database, concluded that testosterone replacement therapy was linked to an increase in of 100% in the risk of heart attack in men aged 65 or over, especially when at the lower age limit and with a previous history of heart disease (Corona; Torres; Maggi, 2020). Accordingly, Lincoff et al. (2023), reported 372 primary outcome events, more than all previous TRT clinical trials combined, and in their population, approximately half of the patients were 65 years of age or older and the majority also had CV disease prior to the study. From this discussion, the possibility arises of questioning CV risk considering populations with specific underlying CV diseases.

With regard to pre-existing CV diseases and TRT, it is contraindicated for men with a recent record (< 4 months) of myocardial infarction or cerebrovascular accident (CVA) and severe heart failure (NYHA Class III or IV) or decompensated are included in hormonal treatment (Kanakis et al. 2023). On the other hand, in the context of HF, low survival still persists, making it necessary to search for new mechanisms to control the disease. Thus, the concept arises that the progression of heart failure (HF) may be affected by reduced anabolic drive, which leads to anabolic/catabolic instability. More specifically, the levels of Insulin-Like Growth Factor 1 (IGF-1), Dehydroepiandrosterone Sulfate (DHEA-S) and total Testosterone (TT) are immensely linked individually to health condition, physical performance and survival. Among the relevant trials, results were found such as reduction in systemic vascular resistance, increase in cardiac output, reduction in QT interval widening in HF, significant increase in the incremental walk test and quality of life score indices, improvement in symptoms in at least one functional class, in the group using testosterone.

In addition, TT was considered safe in general, with no change in relation to: handgrip strength, skeletal muscle volume by transverse computed tomography, or Tumor Necrosis Factor (TNF) levels. In contrast, opposite results were found in a current meta-analysis, which denied the hypothesis that physiological TT levels are related to an improvement in cardiac function, exercise capacity, quality of life or prognosis in HF (Cittadini; Isidori; Salzano, 2022).

With regard to monitoring through laboratory and complementary tests, it is important to separate recommendations for diagnosis from recommendations for monitoring damage to other systems. Among the numerous clinical and laboratory repercussions caused by hypogonadism that are potentially correctable by TRT, some require specific monitoring both to guide therapy and to manage risks. The two scenarios, hypogonadism and TRT, are responsible for the variation in levels

not only of dihydrotestosterone (DHT) or testosterone, but also of other laboratory parameters, mainly: hematological indices, with emphasis on hematocrit; determinants of bone mineralization; and, prostate specific antigen (PSA) values in patients with prostate cancer (PCa). Elevation of hematocrit above the upper normal limit is the most common adverse effect of TRT, being responsible for an increased risk of venous thromboembolism (VTE) (Cannarella et al., 2024). Based on this, it is recommended to measure hematocrit before testosterone replacement and monitor its value during treatment. If values above the threshold are detected, the recommendation is that TRT be suspended until adequate adjustment of hemoconcentration. (Kanakis et al. 2023). Corroborating this proposition, Corona, Torres and Maggi (2020) observed that TRT-related VTE events were often linked to a state of thrombophilia and undiagnosed hypofibrinolysis. A second component to be considered in the continuity of care for patients with reduced testosterone is bone health, which must be continuously investigated during the course of treatment with standard tests for osteoporosis (dual energy radiological absorptiometry – DXA) and assessment of the risk of fall.

Older studies indicated that the use of testosterone leads to an increase in prostate cancer. On the other hand, more recent studies indicate that this interaction is subtler, given this uncertainty, for patients who can receive TRT, that is - with Low-risk, localized prostate cancer with a Gleason score < 7 - it is mandatory to strictly monitor prostate-specific antigen (PSA) concentrations and obtain a urological opinion if PSA measurement > 4 ng/mL and presence of changes on digital rectal exam (Kanakis et al. 2023).

A unique result establishes the influence of the route of administration of TRT on CV risk, especially in the subgroup of oral formulation of replacement therapy. Intramuscular TRT maintains serum DHT levels, which are related to reduced CV risk. On the other hand, higher levels of DHT are more frequently caused by oral or transdermal use, the latter causing less risk than the oral route and a greater risk for IM. No significant effects on CV risk were identified with either injectable or transdermal TRT. The risk-defining variable, which is modified by the route of administration, is the interval between serum DHT and testosterone levels. Oral and transdermal administration methods of TRT have been found to produce greater DHT elevations compared to intramuscular administration (Borst et al., 2014). Contrasting with what the previous study suggests, Gagliano-Jucá and Basaria (2019) state that the intramuscular route of administration presented an increased risk of: stroke, stable angina and acute myocardial infarction. It is important to highlight that the population analyzed did not only include elderly people, more than 500 thousand men aged 18 or over were monitored.

FINAL CONSIDERATIONS

The assessment of CV risks associated with testosterone replacement therapy in men is in its infancy, a fact linked to the extensive limitations of the clinical trials that set out to analyze the topic. It is evident that the increase in harmful effects inherent to therapy is related to multiple factors, therefore, the prescription of said therapy must be based on the correct choice of the route of administration of the exogenous hormone, on the assessment of individual CV risk and previous comorbidities, as well as monitoring through laboratory and complementary tests. The importance of detailed, placebo-controlled, long-term clinical trials that provide consistent data in the investigation of exogenous hormone replacement and outcomes associated with CV risks is highlighted. Although TRT

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shows significant benefits in improving symptoms and hormonal parameters, careful and individualized assessment of CV risks is critical to the safety and effectiveness of this therapy in men with androgenic deficiency.

REFERENCES

AHMED, Talha; ALLATAR, May; PANTALONE, Kevin; HAQUE, Reyaz. Is testosterone replacement safe in men with cardiovascular disease? **Cureus**, v. 12, n. 3, 2020.

BLACKWELL, Kelli; BLACKWELL, Michele; BLACKWELL, Thomas. Testosterone replacement therapy and cardiovascular disease: balancing safety and risks in hypogonadal men. **Current Cardiology Reports**, v. 25, n. 10, p. 1157-1163, 2023.

BORST, Stephen *et al.* Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. **BMC Med**, v. 12, p. 211, 2014.

CANNARELLA, Rossella *et al.* Testosterone replacement therapy and vascular thromboembolic events: a systematic review and meta-analysis. **Asian Journal of Andrology**, v. 26, n. 2, p. 144-154, 2024.

CITTADINI, Antonio; ISIDORI, Andrea M.; SALZANO, Andrea. Testosterone therapy and cardiovascular diseases. **Cardiovascular Research**, v. 118, n. 9, p. 2039-2057, 2022.

CORONA, Giovanni; TORRES, Luiz Otavio; MAGGI, Mario. Testosterone therapy: what we have learned from trials. **The journal of sexual medicine**, v. 17, n. 3, p. 447-460, 2020.

GAGLIANO-JUCÁ, Thiago; BASARIA, Shehzad. Testosterone replacement therapy and cardiovascular risk. **Nature Reviews Cardiology,** v. 16, n. 9, p. 555-574, 2019.

GENCER, Baris *et al.* Cardiovascular risk and testosterone–from subclinical atherosclerosis to lipoprotein function to heart failure. **Reviews in Endocrine and Metabolic Disorders**, v. 22, p. 257-274, 2021.

HADDAD, Rudy M. *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. In: Mayo Clinic Proceedings. **Elsevier**, 2007. p. 29-39.

JHAWAR, Nikita; CHIRILA, Razvan. A review of testosterone supplementation and cardiovascular risk. **Romanian Journal of Internal Medicine**, v. 61, n. 1, p. 35-40, 2023.

KANAKIS, George A, *et al.* EMAS position statement: Testosterone replacement therapy in older men. **Maturitas**, v.178, p. 107854, 2023.

KHARABA, Zelal Jaber *et al.* Testosterone therapy in hypogonadal patients and the associated risks of cardiovascular events. **Biomedicine & Pharmacotherapy**, v. 129, p. 110423, 2020.

KHERA, Mohit; MINER, Martin; JAFFE, Jonathan; PASTUSZAK, Alexander. Testosterone therapy and cardiovascular risk: a critical analysis of studies reporting increased risk. **The journal of sexual medicine**, v. 18, n. 1, p. 83-98, 2021.

LINCOFF, A. Michael *et al.* Cardiovascular safety of testosterone-replacement therapy. **New England Journal of Medicine,** v. 389, n. 2, p. 107-117, 2023.

LOO, Simone Y, *et al.* Cardiovascular and cerebrovascular safety of testosterone replacement therapy among aging men with low testosterone levels: a cohort study. **The American Journal of Medicine**, v. 132, n. 9, p. 1069-1077. e4, 2019.