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TESTOSTERONE REPLACEMENT THERAPY IN MEN WITH HYPOGONADISM AND CARDIOVASCULAR RISK: A SYSTEMATIC REVIEW

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Abstract: Evidence on the relationship between hormone replacement therapy in men with hypogonadism and cardiovascular risk is controversial. We sought to evaluate the effects of hormone replacement therapy on cardiovascular risk in men with hypogonadism. For this systematic review, we used the search tools PubMed, SCIELO, The Lancet and The New England Journal of Medicine for studies published in the databases with emphasis on 2018 and onwards, both in Portuguese and English. The descriptors used were: Hypogonadism, Testosterone, Hormone Replacement Therapy, Heart Disease Risk Factors, Testosterone, Hypogonadism, cardiovascular risk. More than 50 thousand articles were found, of which 1,682 were related to the topic, and 33 were selected and analyzed. Given the above, the scientific stigma of TRT increasing the incidence of negative cardiovascular outcomes gradually tends to be replaced by the perspective of cardioprotection and secondary benefits being promoted by TRT. It is concluded that hormone replacement therapy may offer cardioprotective benefits, as evidenced by most studies analyzed from 2022 onwards.
Keywords: Hypogonadism; Testosterone; Hormone Replacement Therapy; Heart Disease Risk Factors.

INTRODUCTION

Male hypogonadism is a common condition characterized by the inability to produce adequate levels of testosterone and/or sperm. It can be classified as primary, with reduced testosterone levels and increased gonadotropins, or secondary, with low testosterone levels and normal or low gonadotropins. Testosterone replacement therapy (TRT) aims to normalize testosterone levels to improve symptoms and quality of life. The diagnosis of hypogonadism requires serum total testosterone levels <300 ng/dL and

the presence of associated symptoms and/or conditions. TRT is also used in elderly men to prevent symptoms of hypogonadism related to physiological decreases in testosterone levels. Studies show that TRT can improve sexual function, bone mineral density, hemoglobin, and depressive symptoms, in addition to reducing weight, waist circumference, LDL cholesterol, triglycerides, and blood pressure, among other benefits. Although previous studies have associated TRT with serious adverse events, recent studies suggest that there is no causal relationship between TRT and adverse cardiovascular outcomes. (HACKETT et al., 2023; VIGEN et al., 2013; LINCOFF et al., 2023)

GOAL

We sought to evaluate the effects of hormone replacement therapy on cardiovascular risk in men with hypogonadism.

METHODOLOGY

For this systematic review, a comprehensive approach was used to identify studies relevant to the relationship between hormone replacement therapy and cardiovascular risk in men with hypogonadism. We used a variety of research sources, including PubMed, SCIELO, The Lancet, and The New England Journal of Medicine, to conduct specific searches with an emphasis on the years 2018 to 2024.

The search strategy was developed based on terms related to the topic of interest, such as "Testosterone therapy and cardiovascular risk", "Hypogonadism", "Testosterone", "Hormone Replacement Therapy" and "Heart Disease Risk Factors". A combination of these terms was used to maximize the sensitivity of the search and ensure the inclusion of relevant studies.

In PubMed, a total of 450 results were identified using the search phrase "Testosterone therapy and cardiovascular risk", 4,591 results using the term "Hypogonadism", 20,192 results using the term "Testosterone", 5,967 results using the term "Hormone Replacement Therapy", and 45,902 results using the term "Heart Disease Risk Factors", and when using all search phrases with the Boolean operator "AND" we found 100 results, in which 50 results showed that TRT is safe and presents low cardiovascular risk, 20 presented inconclusive results and 30 demonstrated negative outcomes of TRT, all contemplating the period between 2013 to 2024. In SCIELO Brazil, 2 results related to our research were obtained between 2018 and 2024 using the search phrase "Testosterone therapy and cardiovascular risk", 23 results related to the term "Hypogonadism", 103 results related to the term "Testosterone", 24 results related to the term "Hormone Replacement Therapy", and 142 results related to the term "Heart Disease Risk Factors", all from 2018 to 2023.

In the Lancet, 131 results related to research between 2018 and 2024 were analyzed using the search phrase "Testosterone therapy and cardiovascular risk", 116 results related to the term "Hypogonadism", 338 results related to the term "Testosterone", 726 results related to the term "Hormone Replacement Therapy", and 5,531 results related to the term "Heart Disease Risk Factors", all from 2018 to 2024.

The selection of studies was performed following specific inclusion and exclusion criteria, which were previously defined to ensure the relevance and quality of the studies included in the review. Exclusion criteria were carefully designed to ensure the selection of studies that directly addressed the relationship between hormone replacement therapy and cardiovascular risk in men with hypogonadism. In addition, studies that did not present results related to the outcomes of interest, female patients, transgender patients, studies with small sample sizes that limited the generalizability of the results, studies with

inadequate or low-quality methodologies, obsolete studies, and studies that were not available in full text for detailed analysis were excluded. In addition, male patients who were not diagnosed with hypogonadism were excluded, thus ensuring the homogeneity of the study population. These exclusion criteria were applied rigorously and transparently during the process of selecting studies for inclusion in the systematic review.

Relevant data were extracted from the included studies in a systematic and organized manner, using a standardized approach. Data extraction was performed by four reviewers independently, with any disagreements resolved by consensus or consultation with a fifth reviewer, as necessary. This systematic review was conducted in accordance with PRISMA guidelines to ensure transparency and replicability of the processes.

RESULTS

After applying the inclusion and exclusion criteria established in the methodology, a total of 672 potentially relevant studies were identified through searches in the PubMed, SCIELO, The New England Journal of Medicine and The Lancet databases. After the initial screening of titles and abstracts, 149 studies were selected for full text analysis. Of these, 33 studies met all inclusion criteria, were assessed by the members as relevant and evolved for inclusion in this systematic review.

The 33 studies included covered a publication period between 2018 and 2024. The studies were conducted in developed or developing countries, with a geographic distribution that included North America, Europe and Asia. The variety of study designs was wide, including randomized clinical trials, prospective cohorts, case-control studies and systematic reviews with meta-analysis.

The primary outcomes assessed in the included studies were adverse cardiovascular events, such as acute myocardial infarction, stroke, heart failure, cardiomegaly, and cardiovascular death. In addition, several studies also investigated secondary outcomes, such as changes in serum lipid levels, blood pressure, mood changes, depressive symptoms, elevated hematocrit, increased estradiol levels, gynecomastia, and markers of inflammation.

The majority of the studies investigated revealed a neutral association between hormone replacement therapy and cardiovascular risk in men with hypogonadism. Notably, some of these studies suggested a possible cardiovascular benefit associated with the use of hormone replacement therapy, especially in patients with low testosterone levels. This contrasts significantly with studies produced more than a decade ago, which mostly discouraged hormone replacement therapy due to the perceived likelihood of increased cardiovascular risk. However, as of 2018, data indicate a change in this paradigm, suggesting not only the absence of significant risks, but also the possibility of benefits to the cardiovascular system associated with TRT in patients who are duly fit to receive the treatment.

Among the limitations identified in this systematic review, the heterogeneity of the studies included in terms of study populations and definitions of outcomes stands out, which made it difficult to conduct meta-analyses and generalize the results. Also noteworthy is the major change in perspective that TRT has undergone over time, going from being an "enemy" of patient well-being to an "ally" in combating not only hypogonadism, but also several pathologies secondary to this condition. In addition, most of the studies were conducted in specific populations, limiting the applicability of the results to other populations, as is the case in Brazil.

DISCUSSION

It is essential to understand the biological factors that influence the normalization of androgenization. Testosterone plays a fundamental role as the primary sex hormone in men, being crucial for the development of the male reproductive system and secondary sexual characteristics. After being stimulated by luteinizing hormone (LH), testosterone is synthesized from cholesterol through the process of steroidogenesis.

This synthesis occurs mainly in the Leydig cells of the testes, and to a lesser extent in the adrenal glands. The regulation of this process is carried out by the hypothalamic-pituitary-testicular axis, in which increased testosterone levels activate a negative feedback mechanism that inhibits the release of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone, and LH.

Testosterone functions are primarily regulated by the androgen receptor (AR), which binds to specific androgen response elements in the promoter regions of target genes. However, it is becoming increasingly clear that testosterone, like other steroid hormones, also exerts rapidly activating non-genomic actions, possibly through genomic mechanisms independent of the AR and effects mediated by its conversion to other active hormones, such as estradiol and dihydrotestosterone. The importance of AR sensitivity is evidenced by its significant impact on phenotype. Men with increased receptor sensitivity generally have normally low serum testosterone levels, whereas those with reduced AR sensitivity have levels at the upper end of the normal range. In turn, circulating testosterone levels are regulated by feedback on the hypothalamic-pituitary axis. Total testosterone in the circulation includes free, albumin-bound, and sex hormone-binding globulin (SHBG)-bound testosterone. The biologically available active hormone component is considered to be the sum of free and albumin-bound testosterone (bioavailable testosterone), since SHBG-bound testosterone is tightly bound and dissociates slowly, and is considered relatively inactive. Male hypogonadism is a common clinical condition that arises when there is an inability to produce adequate physiological levels of testosterone, normal sperm counts, or both. This condition can manifest as primary (or hypergonadotropic), characterized by reduced testosterone levels and increased gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]); or secondary (or hypogonadotropic), in which there are low testosterone levels, with gonadotropins that are inappropriately "normal" or low.

Testosterone replacement therapy (TRT) consists of normalizing reduced testosterone levels with the aim of improving symptoms and, consequently, quality of life. TRT is indicated for the treatment of hypogonadism exclusively with extensive and complete clinical and laboratory evidence.

Hypogonadism will be diagnosed by measuring serum total testosterone <300 ng/dl and in the presence of symptoms and/or conditions known to be associated with late-onset hypogonadism, such as reduced physical performance, physical changes (loss of body hair, reduction of lean mass, visceral obesity), sexual symptoms (reduced sexual desire and erectile dysfunction, reduced nocturnal erections), cognitive or mood symptoms (depression, sleep disorders), presence of associated conditions (infertility, metabolic syndrome, type 2 diabetes mellitus) and anemia. Late-Onset Hypogonadism, erroneously called Andropause, is a condition associated with aging that begins around the age of 40 or even 30. The rate of decline is approximately 0.4 to 2% per year. From the age of 65, there is an increase in SHBG levels

that results in a disproportionately faster decline in Free Testosterone levels. Late-Onset Hypogonadism is considered a mixed form of hypogonadism, since it originates from the reduction in the number and activity of Leydig cells, as well as a reduction in the secretion pulses of GnRH and LH.

Hypogonadism appears in a second case of a group that benefits from TRT: elderly men. In this case, it is a significant minority of the male population that has Testosterone levels below the averages considered normal. However, it is a fact that circulating testosterone declines with age, in a physiological manner, and TRT is a good alternative to avoid symptoms of hypogonadism when serum levels of the hormone are below normal.

Several studies have shown that men with hypogonadism who underwent TRT demonstrated progressive weight loss, as well as loss of abdominal circumference. It was also proven that there was a reduction in LDL, cholesterol, triglycerides, systolic and diastolic blood pressure, a decrease in serum glucose, an improvement in insulin resistance, a decrease in C-reactive protein and an increase in HDL.

Studies conducted about a decade ago reported that TRT in men with hypogonadism results in life-threatening adverse events, such as: acute myocardial infarction, stroke, deep vein thrombosis, dyslipidemia, atherosclerosis, among others. However, recent studies, such as the one conducted by the US FDA, the TRAVERSE study, have shown that there is no causal relationship between the use of TRT in men with hypogonadism and cardiovascular outcomes. Clinical studies on testosterone replacement therapy (TRT), again including TRAVERSE, have been conducted using specific testosterone preparations, such as testosterone gel and testosterone undecanoate.

However, it is important to note that other testosterone esters, or variations, lack robust evidence to guarantee their safety and efficacy in relation to cardiovascular outcomes and other relevant clinical results.

Testosterone and the more potent dihydrotestosterone (DHT) bind to cytoplasmic androgen receptors (AR), which are assisted by heat shock proteins. After binding, the DHT-AR complex migrates to the nucleus, forms a dimer with another DHT-AR complex, interacts with coactivator proteins and promotes the activation of a family of genes containing androgen response elements, which influence the behavior of myocardial and vascular cells. In addition, there is evidence to support a rapid and direct effect of testosterone on cell membranes through G-protein coupled receptors, resulting in an increase in inositol triphosphate and diacylglycerol, and subsequent changes in the activity of cytoplasmic calcium and potassium channels.

Research has demonstrated the antiatherogenic effect of testosterone, possibly related to its influence on the vascular bed, attributed to its conversion into estrogen by the action of the aromatase enzyme. In addition, some studies suggest that this improvement may also occur through changes in the lipid and inflammatory profile of these patients.

Testosterone inhibits L-type calcium channels, resulting in coronary vasodilation and increased coronary blood flow. Testosterone improves endothelial function, reduces vascular reactivity, prolongs the time to ST-segment depression in men with known coronary artery disease, and shortens the QT interval. Testosterone administration also decreases total, subcutaneous, and intra-abdominal body fat. Testosterone administration increases circulating levels of prothrombotic and antithrombotic factors. It does not significantly affect myocardial infarction size in preclinical models of myocardial infarction.

Studies indicate that TRT was associated with an increase in sexual desire, improved walking ability, and had a small effect on patients' vitality.

Impaired skeletal muscle function and muscle atrophy are features of CHF that may be related to the state of chronic inflammation and insulin resistance that characterize these patients. Another possible mechanism to be considered is the anti-inflammatory effect of testosterone.

Indeed, testosterone has been shown to inhibit plasma pro-inflammatory cytokines such as TNF-α and interleukin (IL)-1β, while promoting anti-inflammatory actions mediated by IL-10. Furthermore, testosterone has been shown to suppress the release of TNF-α, IL-1β, and IL-6 in cultured monocytes from men with hypogonadism and type 2 diabetes. Additionally, testosterone has been shown to reduce the inflammatory response induced by lipopolysaccharide (LPS) and TNFα in endothelial cells. There is evidence that T treatment improves insulin sensitivity and reduces fasting glucose levels in men with CHF and metabolic syndrome or type 2 diabetes.

Testosterone replacement therapy (TRT) reduces depressive symptoms, according to data from small, randomized, placebo-controlled trials in patients with clinically pretreated mild depression. This impact was not observed in men with major depressive disorder. In patients without pre-treatment depression, TRT results in a reduction in depressive symptom scores; however, the clinical value of this is difficult to measure.

Although the exact mechanism underlying testosterone and bone density is not yet fully understood, testosterone plays a crucial role, due to its anabolic effects, in bone growth and maintenance in both women and men. Testosterone stimulates osteoblast proliferation and, at the same time, reduces pro-apoptotic signaling through precise regulation of protein kinase B, while inhibiting parathyroid hormone-induced osteoclast formation. Age-related testosterone deficiency is associated with a decrease in bone mineral density (BMD) and an increased risk of fracture. Considering that osteoporosis is a significant problem in elderly men and that 30% of all hip fractures occur in men, which is associated with an increased mortality compared with women, the prospect of maintaining testosterone levels within the normal range through testosterone replacement therapy (TRT) is attractive. Furthermore, TRT may improve trabecular architecture, as demonstrated in a small exploratory study involving 10 hypogonadal men evaluated by MRI. It is important to note that patients on TRT did not develop osteoporosis and that the effects of TRT may be evident after 2–3 years.

FINAL CONSIDERATIONS

Based on the discussion presented, it becomes clear how important it is to understand the biological factors that govern the normalization of androgenization and the influence of testosterone on the male organism. Testosterone replacement therapy (TRT) has emerged as a fundamental therapeutic intervention to address male hypogonadism, aiming to mitigate signs and symptoms, thus improving the quality of life of patients affected by this medical condition.

Recent studies demonstrate a significant change in the previously established paradigm regarding the association between TRT and cardiovascular risk. While previous studies discouraged TRT due to fear of possible adverse cardiovascular outcomes, current evidence indicates a more favorable outlook. Most studies have found a neutral association between TRT and cardiovascular risk in men with hypogonadism, and some have even

suggested possible cardiovascular benefits associated with the use of TRT, especially in patients with low testosterone levels. Furthermore, the discussion on the positive effects of TRT in several areas of health, such as hematologic, cardiac, arterial, bone, endocrine, psychological and emotional, reinforces the relevance and potential benefit of this therapy for hypogonadal patients. Recent studies highlight the favorable effects of TRT on weight loss, improvement of lipid levels, blood pressure, insulin resistance, skeletal muscle function, bone mineral density and depressive symptoms, among others. The data collected reinforce the view that TRT is safe and potentially beneficial for cardiovascular health in men with hypogonadism, challenging previous perspectives and indicating new directions for future clinical research. However, it is imperative that more studies be conducted to confirm the real effects of TRT and, finally, definitively categorize it as an "enemy", as suggested by older references, or an "ally", according to new evidence. Furthermore, it is essential to expand these findings, especially in long-term studies, in order to provide a solid basis for clinical decision-making.

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