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REVIEW ARTICLE

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Major clinical studies on the relationship between testosterone levels and aging in men: a systematic review

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Abstract

Introduction: After 30 years of age, testosterone levels decline at a rate of 1-2% per year, which correlates with an increased incidence of late-onset hypogonadism diagnosed in middle-aged and elderly men. Testosterone replacement therapy (TRT) is emerging as a promising solution for aging-related problems. **Objective:** This study aimed to present the main clinical studies on the relationship between testosterone levels and aging in men, as well as an analysis of the reduction in physical and metabolic comorbidities. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from August to September 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 86 articles were found. A total of 23 articles were fully evaluated, and 11 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 23 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=77.4%>50%. It was concluded that in the setting of aging in men, late-onset hypogonadism is the clinical entity characterized by low testosterone concentrations associated with clinical symptoms in the absence of organic disease in elderly men. It has been associated with metabolic syndrome, reduced bone mineral density, and increased risk of cardiovascular morbidity and mortality. Although testosterone replacement therapy reverses most of these conditions in young hypogonadal men, the risk/benefit ratio of testosterone replacement therapy in older men is debatable. In middle-aged and older men with hypogonadism and low libido, testosterone replacement therapy for 2 years improved sexual activity, hypogonadal symptoms, and sexual desire, but not erectile function. Furthermore, men with low testosterone, elevated luteinizing hormone, or deficient

estradiol concentrations had increased all-cause mortality. Testosterone treatment aimed at achieving physiological concentrations in middle-aged and older men may improve lean body mass, while exercise training improves lean body mass, aerobic fitness, and strength.

Keywords: Aging. Men. Testosterone. Hormone replacement.

Introduction

Testosterone is an important hormone in maintaining male physiological function. After the age of 30, testosterone levels decline at a rate of 1-2% per year, which correlates with an increased incidence of late-onset hypogonadism diagnosed in middle-aged and elderly men **[1]**. Previous studies have demonstrated links between testosterone deficiency (TD) and age-related comorbidities. As a result, testosterone replacement therapy (TRT) is emerging as a promising solution for aging-related problems **[2,3]**.

Although TRT is widely studied and used to manage late-onset hypogonadism, there is a lack of data from Asian countries that account for 60% of the global population, particularly in lower-middle-income nations. As the aging process of populations in Asia accelerates, the management of TD in elderly men will become a burden on the healthcare system, resulting in a considerable number of undiagnosed and uncontrolled cases **[1]**.

In this context, the natural relationship between testosterone and sexual functions is well established and has been observed in patients undergoing androgen deprivation therapy (ADT) using luteinizing hormone-releasing hormone (LHRH) agonists, gonadotropin-releasing hormone (GnRH) agonists and antagonists, or competitive androgen receptor (AR) antagonists **[4,5]**. Reducing testosterone levels within the therapeutic threshold for ADT to less than 50 ng/dL (1.7 nmol/L) or even below 20 ng/dL (1 nmol/L) may increase the risks of erectile dysfunction and reduced libido by threefold and fivefold to sixfold, respectively **[5]**.

In addition, other aspects of sexuality are also affected immediately after ADT, such as nocturnal erection, sexual motivation, and orgasms **[4,6]**. Similar situations have been found in cases of hypogonadotropic/hypogonadotropic hypogonadal men **[6]**. The prevalence of all types of sexual dysfunctions increases significantly during the aging process **[1,2]** due to the gradual decline of androgens and their metabolites after age 40, as well as the increasing prevalence of other relevant comorbidities, including diabetes and other endocrine disorders, metabolic conditions, and cardiovascular disease (CVD) **[7,8]**.

Furthermore, sexual dysfunctions are often the first signs of TD in older men. In this regard, decreased frequencies of morning erection and sexual thoughts are closely associated with reduced testosterone in men over 40 years of age. The prevalence of disorders related to sexual desire and erectile dysfunction begins to increase when the total testosterone level decreases below 15 nmol/L and 8 nmol/L, respectively. Interestingly, men with <10.4 nmol/L total testosterone and <225 pmol/L calculated free testosterone have a significantly higher risk of decreased morning erections, erectile dysfunction, and low desire, regardless of age **[1-3]**.

Despite this, the direct pathophysiology of testosterone deficiency on sexual function and behaviors has not yet been fully understood. In the brain, testosterone modulates and upregulates the activities of some functional regions related to sexual responses **[5,6]**. Testosterone plays a role in all components of sexual arousal that are associated with respective brain regions, including the temporooccipital, superior parietal, and orbitofrontal cortices, which involve the perceptual-cognitive component of sexual arousal; the cingulate gyrus, inferior frontal regions, and supplementary motor area, which correlate with motivational aspects of sexual behavior; and the insula, anterior cingulate cortex, and claustrum, which control autonomic responses to sexual stimuli. Thus, testosterone deficiency can affect sexual thinking, motivation, and desire **[3,9]**.

Given this, the present systematic review study presented the main clinical studies on the relationship between testosterone levels and male aging, as well as an analysis of the reduction in physical and metabolic comorbidities.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/28/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 09/28/2024.

Data Sources and Search Strategy

The literature search process was carried out from September to October 2024 and developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods

to the present day. The following descriptors (DeCS /MeSH Terms) were used: "Aging. Men. Testosterone. Hormone replacement", and using the Boolean "and" between MeSH Terms and "or" between historical findings.

Study Quality and Risk of Bias

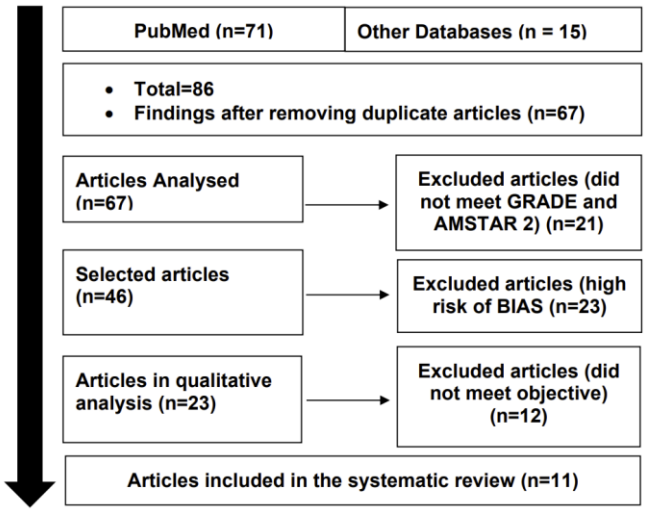
Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

A total of 86 articles were found that were submitted to eligibility analysis, and 11 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=77.4%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 23 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

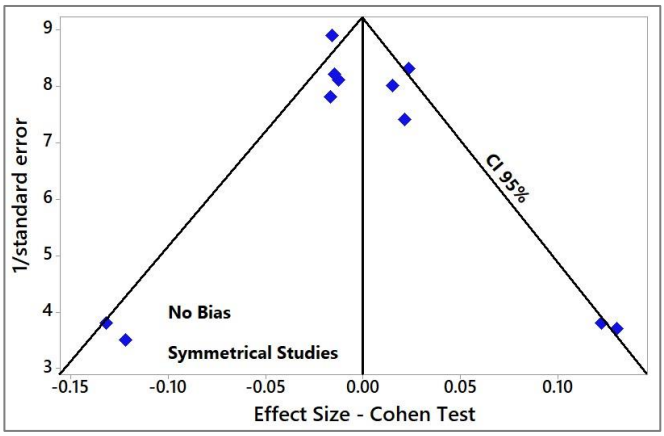
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=11 studies).



Source: Own authorship.

Main Clinical Approaches and Results

After exploring the clinical literature, it has become clear that hypogonadism is associated with a wide range of physical and psychological symptoms that can affect men's overall health **[1-3]**. A 2023 review study **[10]** examined the potential benefits and risks of testosterone replacement therapy (TRT). Testosterone replacement therapy is an effective treatment for hypogonadism, particularly in symptomatic men with low testosterone levels, offering potential benefits such as improvements in symptoms and overall quality of life. However, there are associated risks and side effects that need to be considered.

Sharma et al. (2023) **[11]** assessed the association between sleep duration, sleep quality, and frailty, and determined whether testosterone influenced this association. Men aged 40–79 years were recruited from eight European sites for the European Male Ageing Study (EMAS) and completed a questionnaire. Sleep quality was scored from 0 to 20 and categorized as 0 to 4, 5 to 9, 10 to 14, and 15 to 20, with higher scores indicating poorer quality. A 39-component frailty index (FI) was constructed. A total of 2393 participants

contributed data to the analysis. The mean age was 63.3 years, and the mean sleep duration was 7.01 h. The mean frailty index was 0.15. Mean testosterone levels decreased with decreasing sleep quality. After adjustment, compared with those with a sleep score of 0–4, the FI was 57% (95% CI 38%, 78%) higher among those with a sleep score of 15–20. After adjustment, compared with those with normal sleep duration (6–9 h), those with short (<6 h) and long (≥9 h) sleep duration had a 16% (95% CI 6%, 28%) and 11% (95% CI 0%, 23%) higher FI, respectively. Frailty is associated with impaired sleep quality and duration.

Also, published in 2024 **[12]**, the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Effectiveness ResponSE in hypogonadal men (TRAVERSE) study evaluated the effect of TRT on major adverse cardiovascular events in middle-aged and older men with hypogonadism. The Sexual Function Study, in the original trial, determined the efficacy of testosterone in improving sexual activity, hypogonadal symptoms, libido, and erectile function among men who reported low libido. A total of 5204 men, 45-80 years, with 2 testosterone concentrations <300 ng/dL, hypogonadal symptoms, and cardiovascular disease (CVD) or increased CVD risk were enrolled in the TRAVERSE study; 1161 with low libido were enrolled in the Sexual Function Study (587 randomized to receive 1.62% testosterone gel and 574 to placebo gel for the duration of their study participation). TRT was associated with significantly greater improvement in sexual activity than placebo. TRT improved hypogonadal symptoms and sexual desire, but not erectile function, compared with placebo. Thus, in middle-aged and older men with hypogonadism and low libido, TRT for 2 years improved sexual activity, hypogonadal symptoms, and sexual desire, but not erectile function.

A recent meta-analysis study by Yeap et al. (2024) **[13]** clarified the associations of sex hormones with cardiovascular disease (CVD) outcomes. The independent variables were testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), dihydrotestosterone (DHT), and estradiol concentrations. The primary outcomes were all-cause mortality, CVD death, and incident CVD events. Nine studies provided individual participant data (IPD) (255,830 participant-years). Eleven studies provided summary estimates (n=24,109). Two-stage Random-effects IPD meta-analyses found that men with baseline testosterone concentrations below 7.4 nmol/L (<213 ng/dL), LH concentrations above 10 IU/L, or estradiol concentrations below 5.1 pmol/L had higher all-cause mortality, and those with testosterone concentrations below 5.3 nmol/L (<153 ng/dL) had higher risk of CVD mortality. Lower SHBG concentrations were associated with lower all-cause mortality and lower CVD mortality. Men with lower baseline DHT concentrations had a higher risk of all-cause mortality and CVD mortality, and the risk also increased with DHT concentrations above 2.45 nmol/L. Men with DHT concentrations below 0.59 nmol/L had an increased risk for incident CVD events. Therefore, men with low testosterone, high LH, or very low estradiol concentrations had increased all-cause mortality. SHBG concentration was positively associated and DHT concentration was non-linearly associated with all-cause mortality and CVD.

Authors Kanakis et al. (2023) **[14]** updated the 2015 EMAS statement on TRT in older men with new research on late-onset hypogonadism and TRT through an expert consensus and literature review. Thus, TRT should only be offered to symptomatic older men with confirmed low testosterone concentrations after accounting for uncertainties regarding the long-term safety of this treatment. TRT can be offered to men with severe hypogonadism and erectile dysfunction to improve sexual desire and erectile and orgasmic function. It should also be considered in hypogonadal men with severe insulin resistance or prediabetes mellitus. TRT can also be considered, in combination with proven treatment strategies, for osteoporosis, or selected patients with persistent mild depressive symptoms and/or low self-perceived quality of life, combined with standard medical care for each condition. TRT is contraindicated in hypogonadal men actively seeking fertility treatment. Due to a lack of data, TRT should not be used routinely in older men to improve exercise capacity/physical function, improve cognitive function, or prevent cognitive decline. TRT should be avoided in older, frail men with known breast cancer or untreated prostate cancer all men who have had a myocardial infarction or stroke within the past four months, and those with severe or decompensated heart failure. In addition, short-acting transdermal preparations should be preferred for initiation of TRT in older men, but injectable forms may be considered later. Older men on TRT should be monitored at 3, 6, and 12 months after initiation and at least annually thereafter, or earlier and more frequently if indicated. Obese and overweight patients should be encouraged to undergo lifestyle modifications, including exercise and weight loss, to increase endogenous testosterone.

In addition, Klotho is an anti-aging protein involved in a multitude of biological processes required for healthy aging and offers protection against adverse events such as cardiovascular disease, inflammation, and several types of cancer. Emerging evidence suggests that klotho is also an important component of biochemical pathways that regulate hormonal balance,

which may include pathways governing testosterone production and male sexual health. One study recruited 767 men to quantify the association between serum klotho levels and serum testosterone levels, as well as clinical markers of male sexual health (e.g., testosterone/estrogen ratio, bioavailable testosterone, and free testosterone). A positive association was observed between serum klotho and testosterone. Serum klotho levels were also stratified into quartiles, and statistically significant increases in testosterone were observed for increasing quartile klotho levels using the first quartile as the reference group. The mean testosterone values by klotho quartiles were 306.9 ng/dL, 390 ng/dL, 409.3 ng/dL, and 436.6 ng/dL, respectively. Furthermore, C-reactive protein was inversely associated with testosterone in men and inversely associated with klotho quartiles **[15]**.

Authors Tran et al. (2024) **[16]** analyzed that the cardiovascular safety study of testosterone in men with cardiovascular risk factors or disease found no difference in the rates of major adverse cardiovascular events (MACE) or death, but observed more atrial fibrillation (AF) events in men treated with testosterone. Therefore, these authors investigated the relationship between endogenous testosterone concentrations and the risk of developing AF in healthy elderly men. A posthoc analysis of 4570 male participants in the Aspirin in Reducing Events in the Elderly (ASPREE) study was performed. Men were aged ≥70 years and had no history of cardiovascular disease (including AF), thyroid disease, prostate cancer, dementia, or life-threatening illnesses. The median age was 73.7 (71.6-77.1) years and the median follow-up was 4.4 (3.3-5.5) years, during which 286 men developed AF (15.3 per 1000 participant-years). Baseline testosterone was higher in men who developed incident AF compared with men who did not.

Finally, studies are showing that testosterone therapy can reverse the detrimental impacts of aging. Accordingly, testosterone prescription has increased in recent decades. Middle-aged and older men with low to normal serum testosterone levels are considering testosterone supplementation as an anti-aging strategy. At the same time, there is evidence that physical activity is at historically low levels in the Western world. A study compared the impacts of testosterone treatment aimed at achieving physiological testosterone concentrations in middle-aged and older men. The findings suggest that both testosterone treatment and exercise improve lean body mass in healthy older men. If improving lean body mass is the primary goal, then testosterone treatment may be considered, and the combination of testosterone and exercise may be more beneficial than either alone. In terms of muscle strength in old age, an exercise program is likely to be more beneficial than testosterone treatment. Testosterone treatment aimed at achieving physiological concentrations in middle-aged and older men may improve lean body mass, while exercise training improves lean body mass, aerobic fitness, and strength **[17]**.

Conclusion

In conclusion, in the setting of aging men, late-onset hypogonadism is the clinical entity characterized by low testosterone concentrations associated with clinical symptoms in the absence of organic disease in elderly men. It has been associated with metabolic syndrome, reduced bone mineral density, and increased risk of cardiovascular morbidity and mortality. Although testosterone replacement therapy reverses most of these conditions in young hypogonadal men, the risk/benefit ratio of testosterone replacement therapy in older men is debatable. In middle-aged and older men with hypogonadism and low libido, testosterone replacement therapy for 2 years improved sexual activity, hypogonadal symptoms, and sexual desire, but not erectile function. Furthermore, men with low testosterone, elevated luteinizing hormone, or very low estradiol concentrations had increased all-cause mortality. Testosterone treatment aimed at achieving physiological concentrations in middle-aged and older men may improve lean body mass, whereas exercise training improves lean body mass, aerobic fitness, and strength.

CRediT

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