

## ORIGINAL ARTICLE

# Meta-analysis on the Influence of Testosterone Therapy on Male Kidney Function

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### Abstract

**Objective:** Testosterone plays a significant role in kidney function. Both hypogonadism and hypergonadism, which can affect testosterone levels, have been associated with alterations in kidney function. This review provides a comprehensive and up-to-date overview of the potential impact of testosterone therapy on kidney function among male patients.

**Method:** We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Comprehensive search through Scopus, Embase, and Web of Science databases, with publications included up to June 11, 2023. Eligible studies included adult men aged 18 years and older who received testosterone therapy and reported kidney function outcomes, including randomized controlled trials (RCTs), and observational studies (prospective, retrospective, or case-control). Exclusion criteria included reviews, non-original articles, studies involving non-human subjects, duplicate reports, and studies with insufficient data. Statistical analysis was performed using a random-effects model, and variability was assessed using I<sup>2</sup>. The review protocol was registered with PROSPERO (CRD42023456010).

**Results:** Out of 13 articles, encompassing 39,692 individuals in the treatment group and 10,375 in the control group from studies conducted in seven different countries. The meta-analysis revealed a noticeable difference in age (MD= -0.56; 95% CI: -0.68, -0.45; p<0.001). Testosterone levels were significantly lower in the control group (MD= -0.41; 95% CI: -0.52, -0.30; p<0.001). Baseline blood urea nitrogen concentration was significantly higher in the testosterone treatment group than in the control group, with this difference being statistically significant (MD= 1.66; 95% CI: 1.10, 2.23; p<0.001). Following treatment, blood urea nitrogen was lower in the testosterone treatment group than in the control group, though this difference was not statistically significant (MD= -0.44; 95% CI: -0.93, 0.05; p=0.079). The difference in uric acid levels between the treatment and control groups was not statistically significant (MD= 0.11; 95% CI: -0.02, 0.24; p=0.08). While these non-significant findings may not directly indicate a clinically meaningful impact, they still highlight potential trends that should be explored further, especially considering that BUN and uric acid levels are important markers of kidney function and could be influenced by testosterone therapy over the long term.

**Conclusion:** Testosterone therapy may influence kidney function, though further studies are needed to clarify its long-term effects and clinical significance.

**Keywords:** Kidney Function Tests, Male, Meta-Analysis, Testosterone Therapy.

## 1. INTRODUCTION

Testosterone plays a crucial role in various physiological processes, particularly in male health, including kidney function [1-11]. Understanding the effects of testosterone therapy on kidney function is vital for improving patient care and managing conditions such as hypogonadism and prostate cancer.

Several studies have investigated the relationship between testosterone treatment and kidney function; For instance, one study found that long-term testosterone treatment improved fatty liver and kidney function in men with hypogonadism[12]. These findings align with other reports indicating safe outcomes for cardiovascular, metabolic, and prostate health, suggesting that testosterone treatment may improve kidney function [13-15]. However, conflicting results have also been reported, with some studies suggesting that testosterone may harm the kidneys through glomerular and tubular damage, kidney fibrosis, proteinuria, and hypertensive effects [3]. These contradictory findings highlight the need for further research to better understand the complex relationship between testosterone and kidney function.

Additionally, androgen deprivation therapy (ADT), commonly used in prostate cancer treatment, has been associated with renal impairment. ADT may counteract the vasodilatory effects of testosterone on renal blood vessels, potentially leading to negative impacts on renal tubular function [16]. This highlights the importance of maintaining balanced testosterone levels to support kidney health.

Moreover, research on the influence of sex hormones on renal osteopenia and urinary constituents revealed that testosterone promotes stone formation by suppressing osteopenia in the kidneys and increasing

urinary oxalate excretion, indicating potential implications for individuals at risk of developing kidney stones [17]. A bi-directional Mendelian randomization study using the UK Biobank dataset examined the association between genetically predicted testosterone levels and kidney function. The study found that higher genetically predicted bioavailable testosterone (bioT) in men was associated with an increased risk of chronic kidney disease (CKD) (odds ratio [OR] 1.17, 95% CI: 1.03–1.33,  $p=0.01$ ), albuminuria (OR 1.15, 95% CI: 1.04–1.27,  $p=0.008$ ), and a decrease in estimated glomerular filtration rate (eGFR) (eGFR\_cr:  $-1.70$ , 95% CI:  $-2.09$  to  $-1.31$ ,  $p=2.4 \times 10^{-14}$ ; eGFR\_crcys:  $-1.27$ , 95% CI:  $-1.62$  to  $-0.91$ ,  $p=1.0 \times 10^{-10}$ ). In contrast, genetically predicted total testosterone (TT) levels showed no significant association with kidney function in women, with no effect on CKD (OR 1.02, 95% CI: 0.92–1.14,  $p=0.68$ ) or eGFR (eGFR\_cr:  $-0.24$ , 95% CI:  $-0.49$  to  $0.02$ ,  $p=0.07$ ). These findings suggest a potential link between bioT and kidney function in men but not in women, indicating the need for further investigation into sex-specific effects and underlying mechanisms [18].

The effects of testosterone treatment on kidney function remain complex and not fully understood. While some studies suggest potential benefits, others highlight harmful effects. Given the variability in outcomes, influenced by factors such as testosterone balance, underlying conditions, and genetic differences, it is essential to clarify the relationship between testosterone and kidney function. To address this gap, this systematic review and meta-analysis aimed to investigate the effect of testosterone therapy administration compared to placebo or no therapy on kidney function parameters in male adults.

## 2. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were utilized to construct this systematic review and meta-analysis [19]. The protocol for this meta-analysis was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) web registry (CRD42023456010).

### 2.1 Search Strategy

A thorough search was conducted in the Scopus, Embase, and Web of Science databases using the Polyglot translator, encompassing publications up to June 11<sup>th</sup>, 2023, utilizing the specified terms. We developed our search strategy using Medical Subject Headings (MeSH) terms from PubMed combined with title and abstract terms. For our intervention (testosterone), we utilized MeSH terms such as "Testosterone"[Mesh] and "Testosterone/therapeutic use"[Mesh], along with title and abstract terms like "testosterone therapy," "testosterone replacement," and others.

Regarding the outcome of interest (kidney function), we used MeSH terms such as "Kidney Function Tests"[Mesh], "Blood Urea Nitrogen"[Mesh], and "Glomerular Filtration Rate"[Mesh], as well as title and abstract terms like "GFR," "eGFR," "creatinine," and others. The search strategy was focused on human studies and was not limited by language or time frame.

### 2.2 Study Selection and Screening

After applying our search strategy to the selected databases, the articles were imported into EndNote X9, and duplicates were subsequently removed. The remaining articles were transferred to Rayyan [20], where title and abstract screening, as well as full-text screening, were conducted by two

independent reviewers (A.M.E., M.A.). In cases of disagreement, discussions were held with senior authors A.R.A. and A.Y. until a consensus was established.

### 2.3 Eligibility criteria

The following criteria were used to determine which studies were included in this review: (a) adult men aged 18 years and older; (b) received any form of testosterone therapy; (c) reported pre- and post-treatment kidney function data, including markers such as serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), or other relevant kidney function tests in these male groups, including randomized controlled trials (RCTs) and observational studies (prospective, retrospective, or case-control);

The main interest was the impact of testosterone therapy on kidney function in adult men. The exclusion criteria were as follows: (a) reviews or non-original articles, involving non-human subjects; (b) duplicate reports (including duplicate subject information); and (c) insufficient data.

### 2.4 Data extraction

Four authors (A.M.E., M.A., R.M., and S.E.) extracted variables from the information provided in each study, including the last name of the first author, year of publication, country of the study, and population size. Additionally, detailed information regarding testosterone therapy, such as its name, dose, route, frequency, duration, and measurement, such as ng/dl, was also extracted. Furthermore, data concerning baseline and follow-up levels of testosterone, GFR, eGFR, creatinine, urea, the BUN/creatinine ratio, and uric acid were obtained, along with their respective standard deviations. To ensure accuracy and consistency, two investigators independently reviewed and extracted the data. In cases of discrepancies where a consensus could not be

reached, a third member was involved to facilitate resolution.

### 2.5 Risk of Bias Assessment

Two independent reviewers (M.A., and R.M.) assessed the risk of bias in individual trials. Any disagreements were resolved through discussion, and if necessary, were solved with a third reviewer (A.R.A.). We assessed the quality of the studies based on the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of nonrandomized studies, such as prospective and retrospective studies (e.g., case-control), and the use of the Cochrane Collaboration-developed ROB tool v2 for randomized controlled trials (RCTs) [21].

### 2.6 Outcomes

This study aimed to assess the impact of exogenous testosterone administration on kidney function parameters in males. The evaluated kidney function parameters included creatinine levels, blood urea nitrogen (BUN), glomerular filtration rate (GFR), estimated glomerular filtration rate (eGFR), uric acid levels, and the BUN to creatinine ratio.

### 2.7 Statistical Analysis

The mean difference (MD) with a 95% confidence interval (CI) was calculated to estimate the difference in kidney function parameters between patients receiving testosterone therapy compared to those

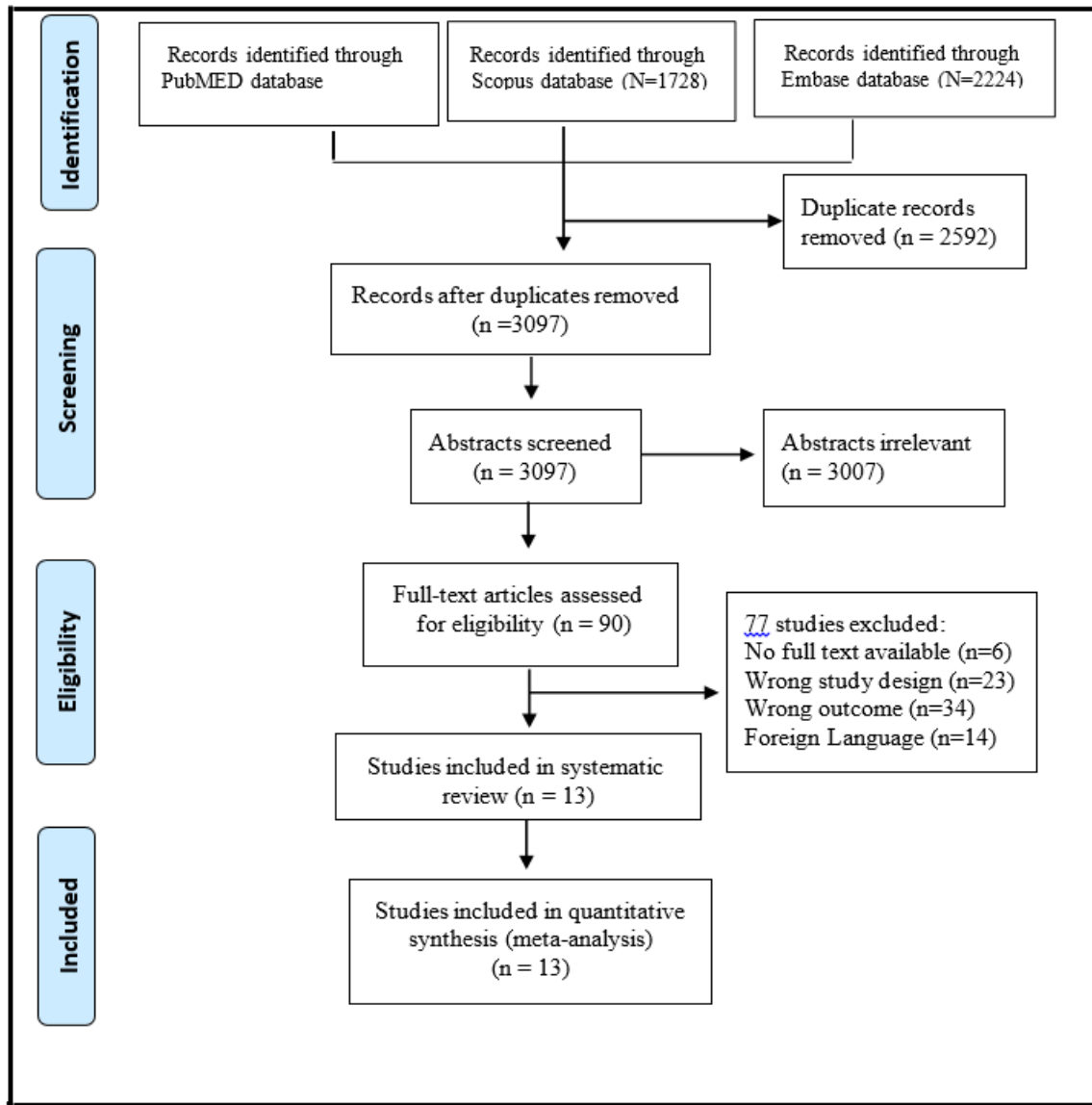
receiving placebo or no therapy using STATA software version 17. To ascertain whether there was variability in the mean difference, Cochran's Q test was used; a significant Q result denoted heterogeneity rather than homogeneity. Using the  $I^2$  statistic, we assessed how much of the total variation may be attributed to study heterogeneity. Additionally,  $I^2$  values of 25%, 25%-50%, 50%-75%, and >75% were used to classify no, minor, moderate, and severe heterogeneity, respectively [22].

To evaluate publication bias, funnel plots with the Egger's regression test were generated [23]. We used forest plots to visually represent the effect estimates from the included research. The threshold for statistical significance was set at  $p < 0.05$  for both ends.

## 3. RESULTS

### 3.1 Literature search

Out of 5689 papers initially screened, 3097 remained after removing duplicates and underwent a full-text analysis. Eventually, 13 studies, involving 8218 patients, were chosen for qualitative synthesis. These studies spanned from 1974 to 2022 in terms of publication years. None of the conference abstracts or reviews met the inclusion criteria; therefore, they were not included in the final selection (**Figure 1**).

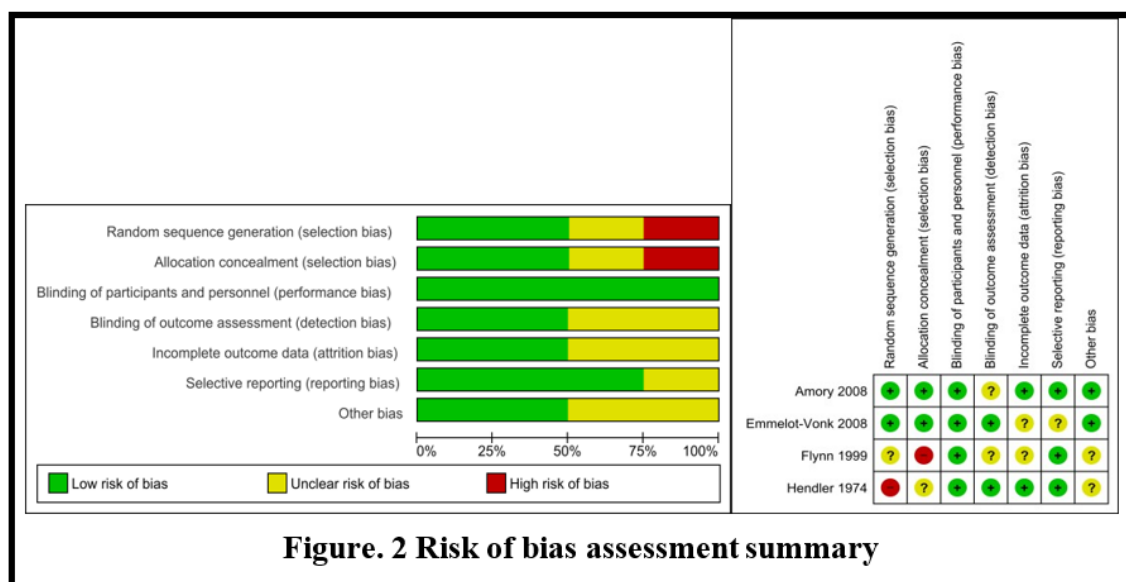


### 3.2 Risk of Bias Assessment

The 5 non-randomized studies were evaluated using the Newcastle-Ottawa scale. Four of them were rated as good quality, and 1 was rated as of poor quality (**Table 1**).

The Cochrane Bias Risk Tool was used to assess the eight randomized clinical trials. The findings indicated a low probability of

bias arising from exclusion and reporting bias. However, the risk of selection bias in these two aspects remains uncertain. The evaluation of two studies suggested an unclear risk of bias, while two studies were identified as having a high risk of bias concerning selection bias (**Figure 2**).



### 3.3 Study characteristics

In total, 13 studies from eight different countries— 1 each from Germany, Iraq, the Netherlands, Poland, Qatar, South Korea, and Sweden, and 6 from the USA were included in 8 randomized controlled trials, 1 cross-sectional cohort, 2 prospective cohorts, and 2 retrospective cohorts. The studies were published from 1974 to 2022. All 13 follow-up period studies had a follow-up period of 1.1- 96 months, and were not reported in 3 studies. Table 1 represents the characteristics of the studies.

### 3.4 Patient and sling characteristics

The focus of this study was hypogonadal older men in 4 (30.7%), hypogonadal men in 5 (38.7%), healthy young men in one (7.7%) study, healthy athletes in one (7.7%) study, adult anemic men with CKD in one (7.7%) study, and healthy men in one (7.7%) study. The patients’ mean age ranged from 23.9 to 77.6 years, and was not reported in 5 studies. In 61.5% of the studies, patients suffered from hypogonadal disease, and four articles (30.7 %) of the studies involved CKD. The details of the general characteristics are reported in Table 1.

**Table 1. Summary included studies**

Author Years	Study design	Patient No.	Population	Purpose	Study Period	Country	Newcastle Ottawa
Alwani, M. 2021 [1]	Prospective	312	Hypogonadal Men (T levels ≤350 ng/dL)	Long-term effectiveness of TTh on renal function	2004-2015	Qatar, Germany	9 (C:2, S:5, O:2)
Emmelot-Vonk, M. H. 2008 [24]	RCTs	113	Hypogonadal Older Men (T levels ≤13.7 nmol/L)	Effects of testosterone supplementation on functional mobility, cognitive function, bone mineral density, body	2004 - 2005	Netherlands	NA

Author Years	Study design	Patient No.	Population	Purpose	Study Period	Country	Newcastle Ottawa
				composition, plasma lipids, quality of life, and safety parameters in older men with low-normal testosterone levels.			
<b>Hajjar, R. R. 1997 [25]</b>	Retrospective	31	Hypogonadal Older Men (bioavailable T levels 72 ng/dL or less)	To determine complications, toxicities, and compliance of long-term testosterone replacement in hypogonadal males	XXX	USA	7 (C:2, S:3, O:2)
<b>Hendler, E. D. 1974 [26]</b>	RCTs	11	Anemic Men with CKD	To determine the safety and efficacy of testosterone in treating anemia in patients on maintenance HD	1972	USA	NA
<b>Morley, J. E. 1993 [27]</b>	RCTs	8	Hypogonadal Older Men bioavailable test <70 ng/dl	To examine the effects of testosterone administration on older hypogonadal males (bioavailable testosterone less than 70 ng/dL)	1992-1993	USA	NA
<b>Skiba, R. 2022 [28]</b>	RCTs	35	Hypogonadal Men with CKD (total T <8mmol/L or total T 8–12 mmol/L and free T < 220 pmol/L)	To evaluate the efficacy and safety of testosterone replacement therapy (TRT) in men with chronic kidney disease and hypogonadism	Ns	Poland	NA
<b>Yeo, J. K. 2020 [29]</b>	RCTs	25	Hypogonadal Men with CKD (Serum T <30ng/dl)	To evaluate the efficacy and safety of testosterone replacement therapy to improve QOL in patients with CKD	Ns	South Korea	NA
<b>Sharma, R.</b>	Retrospective	38706	Hypogonadal	To evaluate the	Ns	USA	7 (C:2, S:3,

Author Years	Study design	Patient No.	Population	Purpose	Study Period	Country	Newcastle Ottawa
2020 [30]			Men with CKD	effectiveness of Safety of using TRT in delaying the progression of CKD			O:2)
Amory, J. K. 2008 [31]	RCTs	10	Health Men	To determine the safety and efficacy of chronic oral TE plus dutasteride for contraception for male hormonal contraception	4 weeks	USA	NA
Abdulhadi, F. 2018 [32]	Cross-sectional	32	Healthy Athletes	Impact of hormones and protein	Jan-Apr 2018	Iraq	6 (C:2, S:3, O:1)
Sahlin, K. B. 2020 [33]	RCTs	30	Healthy Young Men	To gain insight into the effects of changes in testosterone supplement abuse on the liver and kidney function by analyzing routine blood biomarkers in healthy young men undergoing pharmaceutical castration and subsequent testosterone supplementation	Ns	Sweden	NA
Yassin, A. 2020 [34]	Prospective	321	Hypogonadal Men	To evaluate the long-term effectiveness of T therapy on renal function	Ns	Germany	8 (C:2, S:4, O:2)
Flynn, M. A. 1999 [35]	RCTs	20	Healthy Elderly Men	Effect of DHEA on aging men	Ns	USA	NA
<b>Not stated; Ns. Randomized Controlled Trials; RCTs, Not applicable; NA, Newcastle -Ottawa Score; Poor quality (0 or 1), fair quality (2), and good quality (up to 3).</b>							

### 3.5 Age

Age was reported in five studies involving a total of 1,296 individuals [1, 24, 25, 27, 34]. Patients receiving testosterone treatment were younger than those in the comparator

group. The meta-analysis of reported age included 785 patients from the testosterone group and 511 from the comparator group. A heterogeneity test ( $Q=64.5$ ;  $I^2 = 93.8\%$ ;  $p<0.001$ ) indicated significant heterogeneity

among the studies, prompting the use of a random-effects model for statistical analysis. In the testosterone therapy group, the age was significantly lower (MD= -0.56; 95% CI: -0.68, -0.45; p<0.001), as shown in Figure 3.

3.6 Testosterone

Seven studies, encompassing 1,438 patients, reported baseline testosterone levels [1, 24, 25, 27, 28, 33, 34]. Patients receiving testosterone therapy had lower baseline testosterone levels compared to those in the

comparison group. The meta-analysis included 867 patients from the testosterone group and 571 from the comparator group. A heterogeneity test (Q=9.03; I<sup>2</sup> = 96.9%; p<0.001) indicated significant heterogeneity among the studies, necessitating the use of a random-effects model for statistical analysis. Testosterone levels were significantly lower in the controlgroup (MD= -0.41; 95% CI: -0.52, -0.30; p<0.001), as illustrated in Figure 4.

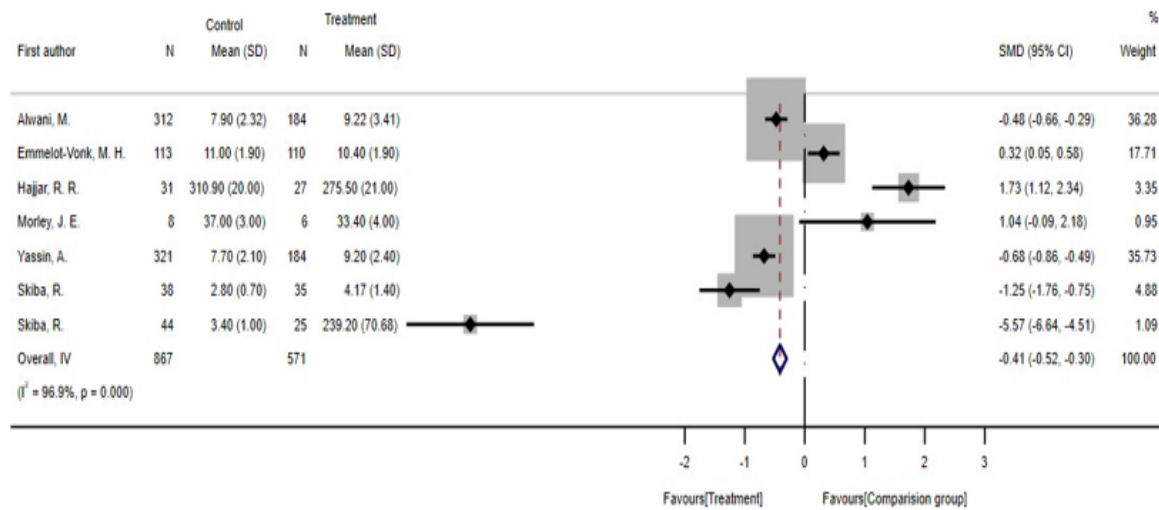


Figure 4. Forest plot of testosterone comparison of testosterone treatment.

3.7 Blood urea nitrogen

Two studies, involving a total of 72 subjects, reported baseline and follow-up blood urea nitrogen (BUN) levels [25, 27]. The meta-analysis included 39 patients from the testosterone group and 33 from the control group. At baseline, patients in the testosterone treatment group had higher BUN levels compared to those in the control group. A heterogeneity test (Q=10.72; I<sup>2</sup> = 90.7%; p=0.001) indicated significant heterogeneity between the studies, prompting the use of a random-effects model for statistical analysis. BUN levels were significantly higher in the testosterone treatment group (MD=1.66;

95% CI: 1.10, 2.23; p<0.001), as shown in Figure 5.

After treatment, patients receiving testosterone therapy had lower BUN counts than those in the control group. A heterogeneity test (Q=192.68; I<sup>2</sup> = 88.9%; p=0.003) again indicated significant heterogeneity, and a random-effects model was used for statistical analysis. Although BUN levels were lower in the testosterone treatment group, this difference was not statistically significant (MD= -0.44; 95% CI: -0.93, 0.05; p=0.079), as illustrated in Figure 6.

3.8 Creatinine

Baseline creatinine levels were reported in

five studies involving 1,314 individuals [1, 12, 24, 25, 32]. The meta-analysis included 801 individuals from the testosterone group and 513 from the control group. Patients receiving testosterone therapy had lower baseline creatinine levels compared to those in the control group. A heterogeneity test ( $Q=298.86$ ;  $I^2 = 98.7\%$ ;  $p<0.001$ ) indicated considerable heterogeneity among the studies, necessitating the use of a random-effects model for statistical analysis. This difference was statistically significant, with creatinine levels being notably lower in the testosterone therapy group (MD= -0.22; 95% CI: -0.33, -0.10;  $p<0.001$ ), as shown in Figure 7.

Treatment follow-up data were reported in three investigations involving 1,224 participants [1, 12, 24]. During the follow-up period, no significant difference was observed between the control group and the testosterone therapy group. A heterogeneity test ( $Q=9.81$ ;  $I^2 = 79.6\%$ ;  $p=0.007$ ) indicated considerable heterogeneity among the studies, leading to the use of a random-effects model for statistical analysis. There was no statistically significant change in creatinine levels between the treatment group and the control group (MD= 0.00; 95% CI: -0.11, 0.12;  $p=0.95$ ), as illustrated in Figure 8.

### 3.9 Urea

Two studies, involving a total of 90 individuals, reported baseline urea levels [25, 33]. The meta-analysis included 35 patients from the control group and 55 from the testosterone group. Patients receiving testosterone treatment had higher baseline urea levels compared to those in the control group. A heterogeneity test ( $Q=49.96$ ;  $I^2 = 98.0\%$ ;  $p<0.001$ ) indicated significant heterogeneity among the studies, prompting

the use of a random-effects model for statistical analysis. Although urea levels were higher in the testosterone therapy group, the difference was not statistically significant (MD=0.25; 95% CI: -0.25, 0.75;  $p=0.326$ ), as shown in Figure 9.

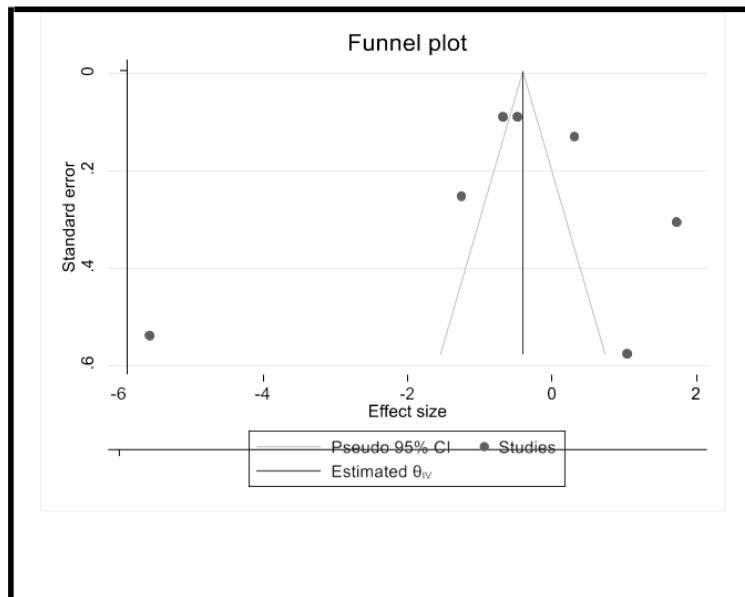
### 3.10 Uric acid levels

Two studies, each involving 1,001 participants, reported baseline and follow-up uric acid levels [1, 12]. The meta-analysis included 368 cases from the control group and 633 patients from the testosterone group. Patients receiving testosterone treatment had higher baseline uric acid levels compared to those in the control group. A heterogeneity test ( $Q=0.85$ ;  $I^2 = 0.0\%$ ;  $p=0.358$ ) indicated no heterogeneity between the studies, allowing the use of a random-effects model for statistical analysis. Baseline uric acid levels were significantly higher in the testosterone therapy group (MD=0.79; 95% CI: 0.66, 0.93;  $p<0.001$ ), as shown in Figure 10.

After treatment, patients receiving testosterone therapy continued to have higher uric acid levels compared to those in the control group at follow-up. A heterogeneity test ( $Q=1.49$ ;  $I^2 = 32.8\%$ ;  $p=0.223$ ) indicated decreased heterogeneity between the studies, and a random-effects model was used for statistical analysis. However, the difference in uric acid levels between the treatment and control groups was not statistically significant (MD=0.11; 95% CI: -0.02, 0.24;  $p=0.08$ ), as illustrated in Figure 11.

### 3.11 Publication bias

A small study impact was identified in the current meta-analysis of five studies (**Figure 12**); the publication bias was calculated using Egger's linear regression test and was -3.44 ( $p = 0.482$ ), which is statistically significant. No proof of publication bias existed.



**Figure.12 Funnel plot of detecting publication bias**

#### 4. DISCUSSION

Testosterone treatment and its effects on male kidney function have garnered significant interest in the medical field. Consequently, we conducted a systematic review and meta-analysis to examine the effects of testosterone therapy on kidney function parameters. Our meta-analysis revealed that control patients had lower testosterone levels compared to the group undergoing testosterone therapy. Additionally, patients in the testosterone group had higher baseline levels of blood urea nitrogen (BUN), urea, and uric acid, and lower creatinine levels than the control group. Post-treatment, while testosterone therapy patients exhibited lower BUN levels and higher uric acid levels compared to the control group, these differences did not reach statistical significance, indicating a lack of strong evidence for a true effect. Similarly, creatinine levels remained unchanged between the two groups after treatment.

These findings align with previous studies highlighting the influence of testosterone on various physiological processes. For instance, research has demonstrated that testosterone can affect the hepatic urea cycle, reducing amino acid nitrogen elimination [36]. Other studies have indicated that testosterone administration can alter blood urea levels, suggesting potential implications for metabolic processes during physical activities [37]. Moreover, the relationship between testosterone and markers such as BUN and creatinine has been explored in different contexts. While testosterone therapy has been associated with lower BUN levels, elevated BUN levels have been linked to adverse outcomes, such as increased in-hospital mortality [38]. Furthermore, the timing of uremia therapy initiation does not correlate with serum creatinine and BUN concentrations, indicating the complexity of managing these markers in clinical settings [39]. In the realm of sports and physical

conditioning, studies have examined the impact of training on biomarkers like urea nitrogen. Athletes engaged in intensive physical activities have been found to exhibit higher BUN levels, reflecting the physiological demands placed on their bodies [40]. Similarly, changes in urea nitrogen values have been noted in volleyball athletes during competition, underscoring the dynamic nature of these markers in response to training and performance [41]. Overall, the interplay between testosterone therapy, urea nitrogen, creatinine, and other related markers is intricate and multifaceted. Understanding these relationships is crucial for optimizing patient care, especially in scenarios involving testosterone therapy. By considering the broader implications of these biochemical changes, healthcare providers can better tailor interventions and monitor patients effectively.

Testosterone, a male sex hormone, is responsible for various physiological processes in both males and females, including the regulation of sex behavior, cognition, mood, and quality of life [42]. Testosterone is primarily produced by testicular Leydig cells [43]. Other cell types, such as testicular macrophages and Leydig-like cells generated from stem cells or fibroblasts, can also produce testosterone [44, 45]. In the general population, low serum testosterone levels have been linked to several cardiovascular and metabolic events, such as diabetes [46-48], stroke [49, 50], metabolic syndrome [47, 51, 52], and atherosclerosis [53]. Low testosterone can also affect muscle mass [54, 55], decreasing serum creatinine levels and kidney function [56, 57]. Moreover, decreased hematocrit can increase the risk of anemia, potentially causing kidney ischemia [58-61]. However, renal function disturbances can be the cause,

rather than the consequence, of developing hypogonadism in patients with chronic kidney disease by affecting the hypothalamic-pituitary-gonadal axis [62, 63] or by causing interstitial fibrosis and calcification of the testis [62, 64]. A meta-analysis by Li et al. [45] aimed to evaluate whether low testosterone levels could independently predict adverse outcomes among male patients with chronic kidney disease (CKD). The meta-analysis found that low circulating testosterone could predict adverse effects in male patients with CKD, suggesting that testosterone levels may affect kidney function. Kurita et al. [60] reported an association between low testosterone levels and reduced estimated glomerular filtration rate (eGFR) in adult men.

Testosterone replacement therapy (TRT) improves various aspects of health in patients suffering from hypogonadism. For example, TRT can improve sexual function and increase muscle mass in young individuals with classic hypogonadism [65]. It also enhances energy levels and libido [66]. These improvements in overall health and well-being may positively affect kidney function in hypogonadism patients. Yassin et al. [12] found that long-term testosterone treatment improved kidney function in men with hypogonadism, showing benefits for fatty liver and kidney function while maintaining cardiovascular, metabolic, and prostate health. Several mechanisms can explain the role of testosterone therapy in benefiting kidney function, such as its vasodilatory effects on renal blood vessels and the improvement of renal tubular function [16]. It may also have glycemic benefits in men with hypogonadism and type 2 diabetes mellitus, reducing the risk of ischemic renal injury [67, 68]. Additionally, testosterone therapy can positively impact renal function

by improving iron metabolism and availability [18]. To fully understand the effects of testosterone therapy on kidney function among healthy adults and athletes, more research is needed. Some studies have reported harmful effects and elevations in creatinine after starting testosterone therapy in healthy men [24, 32], while others have reported no change in kidney function after treatment [31].

Our results show promising effects of testosterone treatment among males in general. However, while our study provides insights into the relationship between testosterone treatment and kidney function, it is essential to consider other factors that may influence kidney health. For example, a study by Corona et al. [68] discussed the overall benefits of testosterone therapy, including improvements in erectile function and libido. TRT has been extensively studied in various contexts, including its effects on kidney function, glomerular filtration rate (GFR), and sexual functions. Several studies have highlighted the potential benefits of TRT in improving sexual function in hypogonadal individuals [69-73]. TRT has shown positive effects on sexual function, mood, bone mineral density, body composition, and signs of mental and sexual functions in men with low testosterone levels [74]. Moreover, TRT has been associated with improvements in sexual function, libido, and erectile dysfunction in hypogonadal men [75-77]. Studies have also indicated that TRT can enhance sexual responsiveness by improving blood flow and lubrication [78]. Furthermore, TRT has been linked to improvements in cardiovascular health, metabolic control, muscle strength, and overall quality of life in individuals with hypogonadism [79-81]. Overall improvement in metabolic parameters and cardiovascular health

associated with TRT could indirectly benefit kidney function. However, more research focusing specifically on the effects of TRT on kidney function and GFR is warranted to draw definitive conclusions in this regard.

Finally, the available literature suggests that TRT can have a positive impact on sexual functions, including libido, erectile function, and overall sexual satisfaction in individuals with hypogonadism. The potential benefits of TRT extend beyond sexual health to include improvements in metabolic parameters, cardiovascular health, muscle strength, and overall quality of life. While the direct effects of TRT on kidney function and GFR require further investigation, existing evidence supports the notion that TRT can be a valuable therapy for enhancing sexual functions and overall well-being in individuals with testosterone deficiency. However, acne, hirsutism, and a decrease in high-density lipoprotein can also develop following testosterone treatment [82]. Testosterone therapy may be associated with venous thromboembolism, with the risk being highest during the initial months of treatment [83, 84].

The strength of this study lies in its comprehensive search strategy across multiple databases, providing a complete and up-to-date picture of testosterone use for kidney function in both hypogonadal and healthy individuals. However, our study has some limitations. Despite the comprehensive search, the number of included studies was low, reducing the statistical power of the analysis. Furthermore, the inclusion of different study designs with varying sample sizes may increase heterogeneity and bias. The generalizability of our findings was also limited, as only men were included in the articles.

#### *4.1 Limitations:*

Several inherent limitations in this study should be acknowledged and considered

when interpreting the results. First, the primary data sources mainly consisted of prospective, retrospective, and cross-sectional studies, which are susceptible to certain limitations such as low-quality documentation, missing data, and selection bias. Additionally, prospective studies may involve significant costs, particularly in large-scale investigations. Another limitation arises from the possibility of loss to follow-up, where participants may drop out or be unavailable for extended periods, resulting in incomplete data and potential bias. Furthermore, participant selection processes may introduce bias if certain groups are more inclined to participate, impacting the generalizability of the findings. Moreover, the inclusion of retrospective studies in the analysis might explain the observed heterogeneity in outcomes, as the data were not initially collected for comparative analysis, leading to variations in treatment protocols and the presence of uncontrolled confounding factors. While cross-sectional studies offer insights into the prevalence of a condition, they cannot discern changes over time or establish the incidence of the condition. Additionally, there is a risk of selection bias if certain groups are more likely to participate, affecting the generalizability of the findings. These limitations underscore the need for caution in interpreting results from cross-sectional studies and emphasize the importance of considering alternative study designs for a comprehensive understanding of complex phenomena.

Second, our systematic review focused on

the proportion of retrospective studies and the small sample size of the included RCTs, limiting our ability to discern differences and increasing the heterogeneity of estimates for each outcome. Third, we identified selection biases in patients receiving different therapies, including variations in performance status and treatment management. Finally, Studies published in languages other than English were excluded, which may introduce language bias and limit the generalizability of the findings.

## 5. CONCLUSION

Testosterone therapy has shown promising effects on kidney function among males. However, there are still studies that have revealed conflicting results regarding its benefits. It is crucial to consider the potential side effects and risks that may accompany the use of testosterone and shape treatment decisions based on the patient's needs. It is also essential to conduct additional studies to increase the strength and significance of the findings regarding the full effect of testosterone therapy to guide physicians toward the best treatment options for their patients.

**Data Availability Statement:** All data analyzed during this study are included in this article, and further inquiries can be directed to the corresponding author.

**Declarations Conflict of Interest:** The authors declare no conflict of interest.

**Conflict of Interest:** The authors declare that they have no conflicts of interest.

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## التحليل تلوي حول تأثير العلاج بالتستوستيرون على وظيفة الكلى لدى الرجال

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### الملخص

**الاهداف:** يلعب التستوستيرون دورًا مهمًا في وظيفة الكلى. وقد وُجد أن كل من قصور الغدة الدرقية وفرط نشاطها، اللذين يمكن أن يؤثرًا على مستويات التستوستيرون، يرتبطان بتغيرات في وظيفة الكلى. تهدف هذه المراجعة إلى تقديم نظرة شاملة ومحدثة حول التأثير المحتمل للعلاج بالتستوستيرون على وظيفة الكلى لدى المرضى الذكور. أجرينا مراجعة منهجية وتحليلًا تلويًا وفقًا لإرشادات PRISMA

**منهجية الدراسة:** بالمراجعات المنهجية والتحليلات التلوية. تم البحث بشكل شامل في قواعد بيانات Scopus, Embase, Web of Science، وشملت الدراسات المنشورة حتى 11 يونيو 2023. تم تسجيل بروتوكول المراجعة في PROSPERO (CRD42023456010). شملت المراجعة 13 دراسة، حيث كان هناك 39,692 فردًا في مجموعة العلاج و 10,375 النتائج: فردًا في مجموعة التحكم، وتم تنفيذ الدراسات في سبع دول مختلفة. كشف التحليل التلوي عن فرق ملحوظ في العمر (MD= -0.56; p<0.001). كما كانت مستويات التستوستيرون أقل بشكل ملحوظ في مجموعة العلاج بالتستوستيرون (MD= -0.41; p<0.001). وُجد أن تركيز نيتروجين يوريا الدم الأساسي كان أعلى بشكل ملحوظ في مجموعة العلاج بالتستوستيرون مقارنةً بمجموعة التحكم، وكان هذا الفرق ذا دلالة إحصائية (MD= 1.66; p<0.001). كان مستوى نيتروجين يوريا الدم أقل في مجموعة العلاج بالتستوستيرون مقارنةً بمجموعة التحكم، لكن هذا الفرق لم يكن ذا دلالة إحصائية (MD= -0.44; p=0.079). أما الفرق في مستويات حمض اليوريك بين مجموعتي العلاج والتحكم، فلم يكن ذا دلالة إحصائية (MD= 0.11; p=0.08).

**الاستنتاج:** أظهر العلاج بالتستوستيرون تأثيرات واعدة على وظيفة الكلى لدى الرجال. ومع ذلك، هناك حاجة إلى مزيد من الدراسات لتعزيز قوة ودقة هذه النتائج، مما يساعد الأطباء في اختيار أفضل الخيارات العلاجية للمرضى الذكور.

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