La Vignera et al. Top Ital. sci. j. 2025;3(1)
https://doi.org/10.62684/CDPX9103

Top Italian Scientists Journal

Open Access | Editorial | Clinical Sciences

ISSN 3033-5132

Testosterone Therapy in diabetic and non-diabetic patients with Chronic Kidney Disease: growing interest and potentially new therapeutic implications.

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Published: 6 Jan 2026

Abstract

This is a short editorial summarizing a highly relevant clinical problem from an epidemiological perspective i.e. the possible pathophysiological links between testosterone deficiency (hypogonadism) in males, a condition known as hypogonadism, and renal function in patients with chronic kidney disease. While these two conditions may share important pathophysiological links, in clinical practice they are mostly considered unrelated. Testosterone hormone replacement therapy (HT) may likely help reduce the progression of chronic kidney disease, although patient phenotyping and the recognition of potential diagnostic biases must be considered to avoid risks.

Editorial

Testosterone is the primary male sex hormone involved in the development and function of the male reproductive system. It is also a key hormone in maintaining muscle mass, bone density, hematocrit, healthy mental status and overall energy levels. Testosterone levels decrease naturally with the age, however chronic health conditions, such as obesity and/or inflammation can accelerate its decline [1]. Testosterone deficiency, referred as hypogonadism, is associated to diverse physical complaints and psychosocial problems [2]. Testosterone deficiency may actually start very early in obese children (Mancini M…….Folli F, JCEM)

There is evidence that hypogonadism occurs in at least 30% of men with type 2 diabetes (T2D) and it is associated to an increased risk of cardiovascular and all-cause mortality [3].

Diabetes increases the risk of kidney and cardiovascular disease through hyperglycemia and low grade chronic inflammation, which damage blood vessels and organs. Daniele G……Folli F. Acta Diabetologica 2014 o 2015; Monroy A……Folli F, Diabetologia 2009; Tripathy D, Daniele G ….Folli F 2014 on 2015, Diabetologia [4]. Hyperglycemia damages renal capillaries causing protein loss, as well as causes the increase of reactive oxygen species and inflammation, that are responsible of the onset of diabetic nephropathy and atherosclerotic plaques in the heart. These events determine organ damage and increase the risk of heart failure, heart attack, and stroke. Brownlee M, Nature (Review) 2004 o 2005; Fiorentino TV……..Folli F, 2014 o 205 Current …….Review

Hypogonadism is both a complication of diabetes and a risk factor for it, possibly creating a vicious cycle possibly worsening kidney and heart disease, and thus increasing mortality and morbidity [3,5]. This condition in diabetic people can be associated to obesity, very high C-reactive protein levels and mild anemia, along with the prevalence of typical symptoms of hypogonadism (fatigue and erectile dysfunction) [6].

A possible relation between Chronic Kidney Disease (CKD) and hypogonadism emerged from recent evidence. CKD is a chronic, progressive disease with a gradual glomerular disfunction. It remains a primary international public health issue, involving more than 10% of the world's population with an increase in cases expected to rise [7]. It has a multifactorial nature, whose possible causes are associated with diabetes, hypertension and autoimmune diseases [8]. Evidences indicate that the likelihood of developing hypogonadism is higher in individuals with CKD than in the general population [9]. A meta-analysis assessing the relationship between CKD and serum testosterone levels reports lower hormone concentration in CKD patients compared with more unfavorable prognoses compared to non-CKD population [10]. The relationship between hypogonadism and CKD

is supposed to be bidirectional, in the sense that each condition can reciprocally influence and worsen the other.

Low testosterone level was considered as a potential risk factor that can induce renal failure in men. About 50%-70% of men affected by severe CKD manifest hypogonadism considering low levels of both total and free testosterone [11].

In a long term follow-up (11.2 years) study, the incidence and hazard ratio of CKD was higher among male hypogonadal adults (21/1000, 95% CI: 18/1000, 25/1000) compared to those with low and normal levels in their elderliness (18/1000, 95% CI: 16/1000, 22/1000, P = .2) [12]. In non-dialysis CKD men the reduction in endogenous testosterone concentration manifested with progressive CKD was linked to endothelial dysfunction. and increasing the risk of cardiovascular events [13].

Several mechanisms have been proposed to explain this relationship. In case of CKD, gonadal function may be compromised by uremic environment that interferes with the hormones synthesis at level of Leydig cells (primary hypogonadism) and centrally at the level of the hypothalamic-pituitary-gonadal axis (HPG) (secondary hypogonadism), disrupting its production [1]. Likewise, nutritional deficiencies [14] such as lack of proteins, iron, vitamin D, imbalances of potassium, phosphorus and sodium, as well as the increase of inflammatory cytokines (TNF-alpha and IL-6) in CKD [15] interferes with the HPG axis, reducing the release of testosterone. Anaemia, which is a frequent complications of CKD condition [16], affects negatively endogenous testosterone levels. CKD also alters the metabolism of sex hormone-binding globulin, reducing the amount of free testosterone in the blood [1].

Equally, low testosterone levels may determine profound risks in cases of CKD, such as infertility and loss of libido, reduction of muscle mass and bone loss, anemia, compromise quality of life and increase the risk of cardiovascular disease [17].

Epidemiological data from observational and clinical trials demonstrate an overlap between metabolic, cardiovascular, and renal diseases, referred as “cardio-renal-metabolic disease (CMR)”, where the manifestation of one rises the risk and worse the effects of the others. The pathophysiological mechanisms that interfere with these three diseases are the same, and when activated triggers a vicious cycle, that maintains and prolongs the diseases, and causes morbidity and mortality [18].

Testosterone acts on the cardiovascular system, exerting protective actions. Due to its activity on endothelial function, cholesterol levels and blood pressure, testosterone causes increased vasodilation and reduced atherosclerotic plaque formation in some populations. In the TRAVERSE trial, testosterone did not increase the rate of events as compared to placebo in men with preexisting or a

high risk of cardiovascular disease, who present symptoms of hypogonadism, ie elderly men with an already compromised clinical picture [19].

In this context, testosterone therapy (TRT), beyond the classic androgenic effects, may have benefits in renal and cardiovascular protection in a high-risk population.

The mechanism underlying the beneficial effects of testosterone on kidneys is not completely understood, but it is likely to be due to its activity on vasodilation in renal vessels, increase of the production of nitric oxide (NO), reduction of inflammation [20]. Testosterone promotes erythropoiesis [21], contrasting the anemia common in CKD, which if often worsened by testosterone deficiency.

Evidence from meta-analysis of observational studies [22] and RCT [23] show that testosterone replacement therapy (TRT) positively impacts body composition with a reduction in fat mass and an increase in lean mass as well as acts on insulin sensitivity and oxidative metabolism in men with diabetes. TRT in hypogonadal men with CKD potentially might improve sexual health, mood [24], and physical abilities for its activity on bone and muscle mass [25], contributing to better mental health and overall wellbeing, offering advantages that goes beyond its possible benefits on CKD.

A large real-world cohort by Bonnet et al., reported the effects of testosterone therapy on acute kidney injury (AKI) and kidney failure in diabetic individuals with hypogonadism in comparison to matched individuals not undergoing testosterone therapy [26]. This study, based on TriNetX Research Collaborative Network, involved almost 52,000 diabetic individuals with hypogonadism. After propensity-score matching, the group of diabetic men with hypogonadism that received the therapy with testosterone showed a reduced risk of AKI (HR 0.93; confidence interval [CI] 0.87–0.98; $p = 0.01$) a reduced risk of renal failure with replacement therapy (HR 0.81; CI 0.72–0.92; $p = 0.001$), and significant reductions in heart attack (HR 0.85), stroke (HR 0.88), atrial fibrillation (HR 0.91), and total mortality (HR 0.85) in comparison to the untreated population.

These findings suggest that in patients with diabetes and hypogonadism, TRT may have important benefits that surpass the symptoms of hypogonadism, and could positively impact renal and cardiac key outcomes such as acute kidney disease, severe renal failure requiring dialysis/transplantation, cardiovascular events, and mortality. According to the authors, these beneficial effects are associated with various processes promoted by testosterone, including increased erythropoiesis, improved renal oxygenation, vasodilatory effects, modulation of the renin-angiotensin system [26].

The proposed physiopathological mechanisms are supported at least in part by experimental studies, but a specific trial enrolling diabetic men with CKD and hypogonadism has not been reported so far.

The results of this study are encouraging and involve a wide sample size, however due to the nature of design, they must be considered with caution.

These effects could have important clinical implications, in terms of in depth/active evaluation of hypogonadism in diabetics. The hypothesis that hypogonadism, known to be a condition quite common in males with diabetes, is not just a secondary hormonal problem, but potentially a risk factor, that can be modified for reducing renal and cardiovascular complications, is corroborated by these findings. Furthermore, in light of these outcomes, testosterone therapy could be considered as part of integrated treatment. In patients with diabetes and documented low testosterone, TRT could be considered not only to improve symptoms such as libido, muscle mass, and well-being, but also as a possible treatment to reduce the risk of kidney disease and cardiovascular disease. The putative reduction in the burden of kidney disease would have significant implications, such as improved quality of life, reduced mortality, reduced healthcare costs, and fewer complications associated with dialysis or transplantation.

Part of literature concerning the role of sexual steroids on renal-cardiovascular health, results to be contradictory. According to that, testosterone can cause arterial hypertension-mediated renal injury, because of stimulation of renin-angiotensin-aldosterone system (RAAS), leading an increasing of renal sodium reabsorption along with augmented vascular smooth muscle cell proliferation, that increases vascular resistance. These findings are based on female rat models, and the hypothesis on human females have only speculative value [2, 27]. However, data in men demonstrate that short-term testosterone administration lower aldosterone levels, reducing the concentration of aldosterone synthase [28].

Recently, a systematic literature review on large prospective cohort studies revealed an association between testosterone increased all-cause mortality and cardiovascular disease, by analyzing data from men with total testosterone serum levels below 7.4 nmol and low estradiol serum levels (below 5.1 pmol/L) [29].

Likewise, a meta-analysis including 9 cohort studies on a total of 5331 patients with CKDs showed a negative relationship between total testosterone with all-cause death risk, cardiovascular and infectious events, independently by prognostic factors for adverse clinical events, demonstrating that both total and free testosterone of a low level could be predictive of adverse events for male patients with CKDs [30].

Long-term effects of testosterone undecanoate (TU) were estimated in a observational study by assessing renal function endpoints (serum creatinine, urea, uric acid and glomerular filtration rate - GFR). The study involved 505 symptomatic hypogonadal men (T levels ≤350 ng/dL), of which 321

received TU 1000mg/12 weeks following an initial 6-week interval for up to 12 years, the remaining 184 hypogonadal men that did not receive the treatment were considered as controls [31]. The results revealed that long-term testosterone therapy improved renal function in hypogonadal men, by determining a decrease in serum creatinine (1.14±0.18 to 1.07±0.8 mg/dL), uric acid (6.8±1.5 to 5.5±1.6 mg/dL), urea (47.5±12.0 to 31.7±12.9 mg/dL) and an increase in GFR (86.6±12.8 to 98.5±8.6 mL/min/1.73m2), compared to control group that manifested a slight worsening [31]. Based on this study, improvements in renal function may are responsible for reduction in CVD-related mortality.

Despite these findings demonstrate beneficial effects of testosterone, there is a research gap in the literature related to the relationship in humans between either testosterone level or hormone administration and kidney function, that needs further investigation.

Data on cardiovascular risks of testosterone therapy are controversial; in the past, some studies have suggested a possible increased risk of cardiovascular events in elderly subjects or in subjects with complicated comorbidities [32]. However, no study of TRT has been designed to date or large enough to reliably measure these cardiovascular events.

A secondary analyses of the TRAVERSE trial showed that TRT is associated to higher percentage of new-onset acute kidney injury (RR 1.53, 95% CI 1.07-2.18), whereas no risk of new-onset atrial fibrillation (RR 1.48, 95% CI 0.93-2.37) was found in the same group. The study included 2134 men in each cohort, in which before starting therapy men on TRT had lower testosterone values (207 ± 66 ng/dL, $P < 0.001$) compared to men did not received TRT (246 ±140 ng/dL, $P < 0.001$). Like TRAVERSE trial, TRT could represent a risk of acute kidney injury in hypogonadal men at risk factors of heart disease or pre-existing cardiovascular disease, but without increased risk of atrial fibrillation. This analysis, despite the size of the sample considered, based on large global research database, has limitations due to study design and dependence on reported claims data [33].

Testosterone plays a crucial role in various physiological processes, among which muscle protein synthesis, bone metabolism, and the cardiovascular system. Hence, deficiency of testosterone not only compromises physical well-being, but it also directly affects kidney health and blood pressure. Patients with CKD often exhibit low testosterone levels. This is associated with an increased risk of developing cardiovascular complications. In this context, TRT emerges as a potential strategy to improve the quality of life and overall health of patients with CKD, acting by improving muscle mass, stimulating erythropoiesis, counteracting anemia, and ameliorating insulin sensitivity. However, beyond these potential benefits, the use of TRT in patients with CKD have to be carefully monitored. Potential risks associated to the use of TRT are given by fluid retention, that exacerbate hypertension with consequently hearth failure in compromised population, affecting the evolution of renal diseases

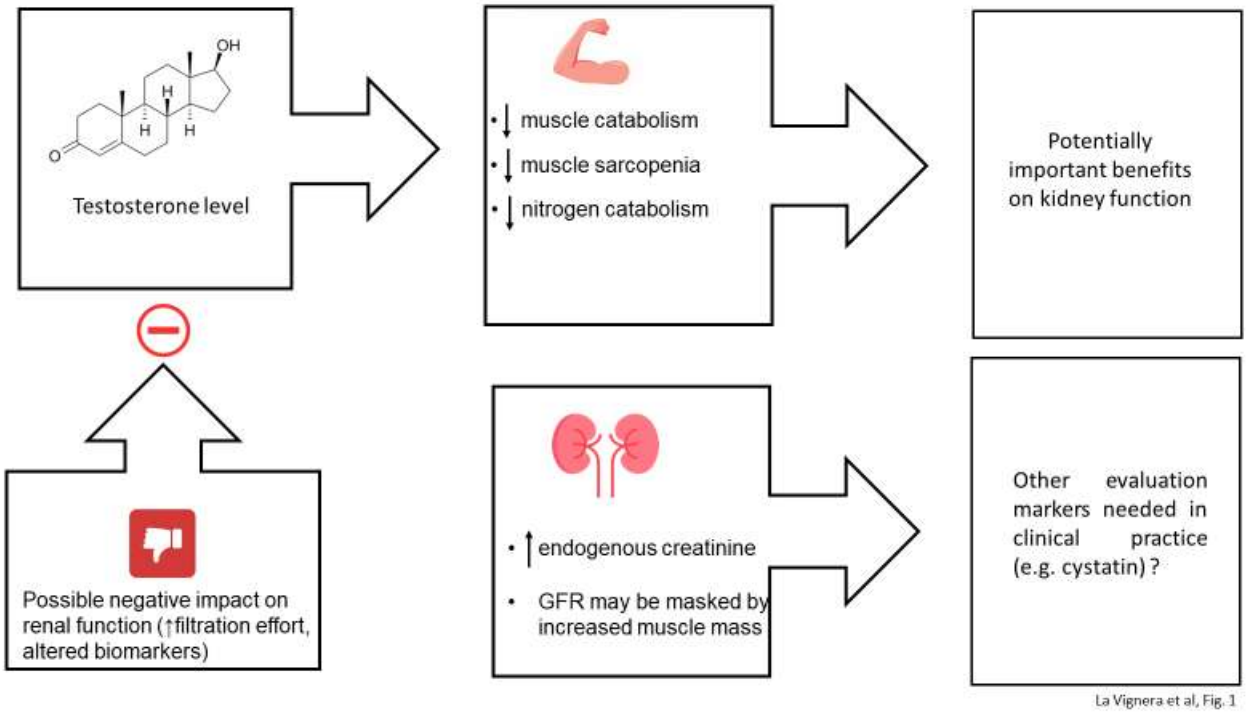
[2]. To translate these results into clinical practice, prospective randomized trials of TRT *versus* placebo on men with diabetes and hypogonadism are needed, with longer follow-up and evaluation of both benefits and risks, such as cardiovascular complications, thromboembolism, prostatic effects, change in renal function,.

The interplay between testosterone deficiency and chronic kidney disease is complex and it is necessary greater attention in clinical practice. If on one hand, TRT offers advantages in the care of patients with CKD, a careful monitoring of the patient and an integrated therapeutic approach, that involves various specialists in the field, are essential to improve the quality of life and clinical outcomes of these patients, and in the same time, reduce potential risks to their renal and cardiovascular health.

Figure 1 Summarizes relationships between testosterone therapy and kidney function. Benefits, potential risks, and potential diagnostic biases.

Figure 1

Relationships between testosterone therapy and kidney function. Benefits, potential risks, and potential diagnostic biases.



Declarations

Conflict of Interest

The authors declare no conflict of interest.

References

1. Zitzmann M (2024) Testosterone deficiency and chronic kidney disease. J Clin Transl Endocrinol 37: 100365. https://doi.org/10.1016/j.jcte.2024.100365.
2. Zitzmann M (2025) Testosteron – „Benzin“ für den alten Mann? [Testosterone-“Fuel” for old men?]. Inn Med Heidelb 66(1):114-123. https://doi.org/10.1007/s00108-024-01824-x.
3. Fallara G, Pozzi E, Corsini C, Belladelli F, Boeri L, Capogrosso P, Montorsi F, Salonia A (2022) Morbidity and mortality in men: Role of androgens. Best Pract Res Clin Endocrinol Metab 36(4):101662. https://doi.org/10.1016/j.beem.2022.101662.
4. Swamy S, Noor SM, Mathew RO (2023) Cardiovascular Disease in Diabetes and Chronic Kidney Disease. J Clin Med 8;12(22):6984. https://doi.org/10.3390/jcm12226984.
5. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E, Maggi M (2011) Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 165(5):687-701. https://doi.org/10.1530/EJE-11-0447.
6. Dandona P, Dhindsa S (2011) Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab 96(9):2643-51. https://doi.org/10.1210/jc.2010-2724.
7. Bikbov B et al (2017) Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 395;10225: 709 - 733. https://doi.org/10.1016/S0140-6736(20)30045-3.
8. Boima V, Agyekum AB, Ganatra K, Agyekum F, Kwakyi E, Inusah J, Ametefe EN, Adu D (2025) Advances in kidney disease: pathogenesis and therapeutic targets. Front Med 12. https://doi.org/ 10.3389 fmed.2025.1526090.
9. Skiba R, Matyjek A, Syryło T, Niemczyk S, Rymarz A (2020) Advanced Chronic Kidney Disease is a Strong Predictor of Hypogonadism and is Associated with Decreased Lean Tissue Mass. Int J Nephrol Renovasc Dis 5;13:319-327. https://doi.org/10.2147/IJNRD.S275554.
10. Pan J, Zheng Z, Mao X, Hu D, Wang W, Liao G, Hao Z (2024) Is There a Two-Way Risk between Decreased Testosterone Levels and the Progression and Prognosis of Chronic Kidney Disease? A

Cohort Study Based on the National Health and Nutrition Examination Survey Database. World J Mens Health 42(2):429-440. https://doi.org/10.5534/wjmh.230110.

11. Albaaj F, Sivalingham M, Haynes P, McKinnon G, Foley RN, Waldek S, O'Donoghue DJ, Kalra PA (2006) Prevalence of hypogonadism in male patients with renal failure. Postgrad Med J 82;972:693–696. https://doi.org/10.1136/pgmj.2006.045963.
12. Amiri M, Fahimeh RT, Rahmati M, Soudmand SA, Behboudi-Gandevani S, Sabet Z, Azizi F (2020) Low serum testosterone levels and the incidence of chronic kidney disease among male adults: A prospective population-based study. Andrology 8:575–582. https://doi.org/10.1111/andr.12728.
13. Yilmaz MI, Sonmez A, Qureshi AR, Saglam M, Stenvinkel P, Yaman H, Eyileten T, Caglar K, Oguz Y, Taslipinar A, Vural A, Gok M, Unal HU, Yenicesu M, Carrero JJ (2011) Endogenous Testosterone, Endothelial Dysfunction, and Cardiovascular Events in Men with Nondialysis Chronic Kidney Disease. CJASN 6(7):1617-1625. https://doi.org/10.2215/CJN.10681210.
14. Iorember FM (2018) Malnutrition in Chronic Kidney Disease. Front Pediatr 6:161. https://doi.org/doi: 10.3389/fped.2018.00161.
15. Kadatane SP, Satariano M, Massey M, Mongan K, Raina R (2023) The Role of Inflammation in CKD. Cells 12(12):1581. https://doi.org/10.3390/cells12121581.
16. Portolés J, Martín L, Broseta JJ, Cases A (2021) Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. Front Med 8. https://doi.org/10.3389/fmed.2021.642296.
17. Romejko K, Rymarz A, Sadownik H, Niemczyk S (2022) Testosterone Deficiency as One of the Major Endocrine Disorders in Chronic Kidney Disease. Nutrients 14(16):3438. https://doi.org/10.3389/fmed.2021.64229610.3390/nu14163438.
18. Marassi M, Fadini GP (2023) The cardio-renal-metabolic connection: a review of the evidence. Cardiovasc Diabetol 22, 195. https://doi.org/10.1186/s12933-023-01937-x
19. Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, Cunningham GR, et al., for the TRAVERSE Study Investigators (2023) Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med 389:107-117. https://doi.org/10.1056/NEJMoa2215025.
20. Alwani M, Al-Zoubi RM, Al-Qudimat A, Yassin A, Aboumarzouk O, Al-Rumaihi K, Talib R, Al-Ansari A (2021) The impact of long-term Testosterone Therapy (TTh) in renal function (RF) among hypogonadal men: An observational cohort study. Ann Med Surg (Lond) 69:102748. https://doi.org/10.1016/j.amsu.2021.102748.

21. Pencina KM, Travison TG, Artz AS, Lincoff AM, Nissen SE, Flevaris P, et al. Efficacy of testosterone replacement therapy in correcting anemia in men with hypogonadism: a randomized clinical trial. JAMA Netw Open 2023;6(10).
22. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, Saad F, Mannucci E, Maggi M (2016) Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Invest 39(9):967-81. https://doi.org/10.1007/s40618-016-0480-2. Epub 2016 May 30. PMID: 27241317.
23. Magnussen LV, Glintborg D, Hermann P, Hougaard DM, Højlund K, Andersen M (2016) Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2 diabetes on metformin monotherapy. Diabetes Obes Metab 18(10):980-9. https://doi.org/10.1111/dom.12701.
24. Corona G, Maggi M (2022) The role of testosterone in male sexual function. Rev Endocr Metab Disord 23(6):1159-1172. https://doi.org/10.1007/s11154-022-09748-3.
25. Zhang W, Cui Z, Shen D, Gao L, Li Q (2025) Testosterone levels positively linked to muscle mass but not strength in adult males aged 20-59 years: a cross-sectional study. Front Physiol 16:1512268. https://doi.org/0.3389/fphys.2025.1512268.
26. Bonnet F, Vaduva P, Halimi JM, Dosda A, Ducluzeau P-H, Koppe L and Fauchier L (2025) Testosterone therapy is associated with reduced risk of acute kidney injury, kidney failure with renal replacement therapy, and cardiovascular events in men with diabetes and hypogonadism. Cardiovascul Diabetol 24:378. https://doi.org/10.1186/s12933-025-02930-2.
27. Komukai K, Mochizuki S, Yoshimura M (2010) Gender and the renin-angiotensin-aldosterone system. Fundam Clin Pharmacol 24(6):687–98. https://doi.org/10.1111 j.1472-8206.2010.00854.x.
28. Goncharov N, Katsya G, Gaivoronskaya L, Zoloedov V, Uskov V, Gooren L (2012) Effects of short-term testosterone administration on variables of the metabolic syndrome, in particular aldosterone. Horm Mol Biol Clin Investig 12(2):401–6. https://doi.org/10.1515/hmbci-2012-0023.
29. Yeap BB, Marriott RJ, Dwivedi G, Adams RJ, Antonio L, Ballantyne CM, Bauer DC, Bhasin S, Biggs ML, Cawthon PM, Couper DJ, Dobs AS, Flicker L, Handelsman DJ, Hankey GJ, Hannemann A, Haring R, Hsu B, Martin SA, Matsumoto AM, Mellström D, Ohlsson C, O'Neill TW, Orwoll ES, Quartagno M, Shores MM, Steveling A, Tivesten Å, Travison TG, Vanderschueren D, Wittert GA, Wu FCW, Murray K (2024) Associations of Testosterone and Related Hormones With All-Cause and Cardiovascular Mortality and Incident Cardiovascular

Disease in Men: Individual Participant Data Meta-analyses. Ann Intern Med 177(6):768-781. https://doi.org/10.7326/M23-2781.

30. Li Li, Huixiang Ju, Hao Jin, Hongmei Chen, Mingzhong Sun, Zhongwei Zhou (2022) Low Testosterone Level and Risk of Adverse Clinical Events among Male Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Cohort Studies. J of Healthc Eng. 2022. https://doi.org/10.1155/2022/3630429.
31. Yassin A, Almehmadi Y, Alwani M, Mahdi M, Jaber A, et al. 2020 Long-term Testosterone Therapy Improves Renal Function in Men with Hypogonadism: A Reallife Prospective Controlled Registry. J Clin Nephrol Res 7(1): 1095. https://doi.org/10.47739/2379-0652/1095.
32. Gagliano-Jucá T, Basaria S (2019) Testosterone replacement therapy and cardiovascular risk. Nat Rev Cardiol 16, 555–574. https://doi.org/10.1038/s41569-019-021.
33. Greenberg DR, Kohn TP, Asanad K, Brannigan RE, Halpern JA (2024) Association of testosterone replacement therapy with atrial fibrillation and acute kidney injury. JSM 21(12):1201–1203. https://doi.org/10.1093/jsxmed/qdae138.