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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Testosterone Replacement Therapy and Cardiovascular Disease: Balancing Safety and Risks in Hypogonadal Men

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Abstract

Purpose of Review The purpose of this review is to analyze the link between testosterone replacement therapy (TRT) and adverse cardiovascular (CV) events.

Recent Findings A few published studies suggest a link between TRT and CV events. These studies contained flaws, and many other studies reveal a reduction in CV events. Hypogonadism is associated with increased mortality in men with CVD. TRT in hypogonadal men can improve many CVD risk factors, reduce QT interval prolongation, lead to better outcomes in heart failure patients, and slow the progression of atherosclerosis.

Summary The use of TRT to achieve physiologic testosterone concentrations in men does not pose a threat to CV health and has demonstrated a cardioprotective effect.

Keywords Testosterone replacement therapy · Cardiovascular disease · Heart · Hypogonadal men · Testosterone · Myocardial infarction

Introduction

In March of 2015, the FDA modified testosterone (T) labeling to indicate an increased risk of heart attack and stroke [1•]. From 2010 to 2014, four studies were published that indicated a link between testosterone replacement therapy (TRT) and increased risk of cardiovascular (CV) adverse events [2–5]. These studies were later found to have major flaws.

The Vigen et al. study was retrospective and found to have substandard statistical analyses, resulting in two post-publications corrections. A second review of the data revealed that those in the TRT group had a 50% reduction in absolute risk for CV events, although the initial publication claimed the opposite. It was also later discovered that nearly 10% of the individuals in the study were women [6].

In the Finkle et al. study, there was no control group to compare the rate of CV events between the TRT group and the untreated group [7]. This study also used prescription information, and there were no records to assess compliance of the study group. There was also no monitoring of T levels, so it is unclear whether the men reached therapeutic T levels [4]. There were also no records of the patients' symptoms [7].

The Testosterone in Older Men with Mobility Limitations (TOM) Trial was stopped prematurely due to increased CV events in the intervention group [2]. The 209 men who were enrolled and randomized in the trial had a high prevalence of CV risk factors at baseline, with 25% having diabetes mellitus, 50% being obese, more than 80% with hypertension, and about 50% of the men had pre-existing heart disease [8]. However, this trial did not have predetermined CV endpoints because the trial was not originally designed to study CV health [9]. The CV adverse events were very diverse, which reduces the odds of these events being due to a single mechanism. There was not a consistent pattern in these events, and the number of overall events were small enough to suggest the possibility that the different rates of CV events between the two trial groups may have been due to chance alone [2].

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Xu et al. published a meta-analysis of 27 placebo-controlled randomized trials lasting longer than 12 weeks, for a total of 2994 middle-age or older men. One thousand seven hundred thirty three of these men were in the testosterone groups, and 1261 were in the placebo group. The conclusion of this meta-analysis was that exogenous testosterone use increased the risk of CV events [5, 10]. The increased occurrence of CV adverse events with testosterone therapy was particularly notable in trials which were not funded by the pharmaceutical industry, although this could be due to chance [5]. Only two of these trials provided a comprehensive list of CV related events by study arm. In some of the trials, it was not clear whether the classification or definition of adverse CV events was made by masked assessors [5]. Several of the smaller studies did indicate that testosterone reduced CV related events, and there were no similar small studies indicating the opposite. Using a forest plot, the authors conclude that the studies were homogenous ($I^2 = 7.8\%$). Using a fixed effect model, the meta-analysis states that testosterone increased the risk of CV related adverse events with an odds ratio of 1.54 (95% CI 1.09 to 2.18) [5]. The authors of this study list many limitations. Analysis by funding and funnel plot indicates that there are possible conflicts of interest in reporting adverse events. Also, some trials only reported serious adverse events, and the severity of events varied between trials [5]. In some testosterone trials, there was the lack of reporting of CV events, and subject drop-out due to increased prostate-specific antigen or polycythemia could cause bias towards the null hypothesis [10].

The number of testosterone prescriptions for men in the USA tripled from 2001 to 2011 [11]. Testosterone therapy has been regarded as controversial due to concerns of increased risk of adverse CV events. A decrease in prescriptions was noted from 2013 to 2016, with the steepest decline shortly after these studies were published and the FDA communication in March of 2015 [1•, 11]. Although these four flawed studies suggested increased CV risk with TRT, over 100 studies have reported reduced CV risk in men with higher endogenous T concentration and improvement of known CV risk factors and reduced mortality in men who underwent TRT [6].

Testosterone Physiology

Testosterone is primarily synthesized from cholesterol in the Leydig cells of the adult testes. The hypothalamic-pituitary-gonadal axis is responsible for regulating sex hormones. The hypothalamus synthesizes and secretes gonadotropin releasing hormone (GnRH) in pulsatile bursts into the hypothalamic-hypophysial-portal circulation. Gonadotrophs of the anterior pituitary synthesize and secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are gonadotropins that control gonadal function [12].

LH is essential for both trophic and acute regulation of steroidogenesis. LH maintains optimal levels of the required enzymes for T synthesis, as well as mobilizes and transports cholesterol into the inner mitochondrial membrane [13, 14]. Testosterone and its metabolites exert their effects by binding to the androgen receptor (AR).

Testosterone's mechanisms of actions can be classified as pre-receptor, receptor, or post-receptor [15]. In the pre-receptor mechanism, T can be converted to dihydrotestosterone (DHT) by 5α-reductase, which binds to the androgen receptor with a greater affinity than T. DHT has a more stable hormone-receptor complex, which allows for the amplification of the hormonal signal [16]. Testosterone can also be converted to estradiol by aromatase [17]. This conversion to estradiol diversifies the action through binding of estrogen receptors [15]. The androgen receptor is encoded by a single gene found at Xq11-12. ARs are found ubiquitously throughout the body [18]. Once the androgen has bound, the AR rapidly translocates to the nucleus, where it acts as a transcription factor [19]. Androgen receptor sensitivity is variable among men and explains the only moderate correlation with T levels and hypogonadal symptoms [20].

It is important to consider variations in the AR. Genetic variability of the CAG trinucleotide repeat on exon 1 of the AR gene is responsible for variations in AR sensitivity [20]. Progressive expansion of this trinucleotide repeat leads to a linear decrease in transactivation function [21]. Differences in the AR gene could explain why some males with testosterone deficiency (TD) are more strongly affected by clinical symptoms than others [20].

Circulating testosterone is primarily bound to sex hormone-binding globulin (SHBG) and, to a lesser extent, serum albumin. Free testosterone is not bound to any serum proteins. Only free testosterone is bioavailable and hence biologically active. This is why some patients may have normal total testosterone and have symptoms of hypogonadism because their SHBG levels may be high and have low levels of free testosterone [22, 23].

Testosterone has many physiologic functions in the body. T is responsible for male primary and secondary sexual development. This includes increasing libido, male hair patterns, voice deepening, and anabolic muscle and bone effects. T also plays a role in erythropoiesis, which leads to males having a higher hematocrit than females [24].

Testosterone's Role in the Heart

In the USA, cardiovascular disease (CVD) is the leading cause of death in men [25]. Variable risk factors for CVD include smoking, sedentary lifestyle, hypertension, obesity, hyperlipidemia, and diabetes mellitus [26]. Even

when coronary heart disease risk factors are considered and adjusted for, the incidence of coronary heart disease is about twice as prevalent in men than it is in women [27, 28]. Hypotheses for this discrepancy include a protective effect of endogenous female hormones, which has been found to increase angiogenesis and vasodilation and decreases reactive oxygen species, oxidative stress, and fibrosis [29].

Testosterone has been shown to alter myocardial and vascular cell behavior [7]. T downregulates L-type voltage-gated calcium channels and upregulates calcium-activated potassium channels, which leads to vasodilatory effects [9].

Testosterone Deficiency

The prevalence of TD ranges from 10 to 40% around the globe [30, 31] and increases with age. TD, or male hypogonadism, arises from disruption at any level of the hypothalamic-gonadal-pituitary axis [32]. While there are various definitions for male hypogonadism from different organizations, the Endocrine Society defines it as a "clinical syndrome that results from the failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic-pituitary-testicular axis" [33, 34]. Hypogonadism can be classified as primary or secondary. In primary hypogonadism, the problem lies at the testicular level. It is classified by elevated gonadotropins, decreased testosterone, and impaired spermatogenesis. Secondary hypogonadism is characterized by low testosterone and low or inappropriately normal gonadotropin levels. Both primary and secondary hypogonadism can be congenital or acquired [32]. Age-related hypogonadism is a result of both testicular failure and hypothalamic-pituitary failure. Leydig cells of elderly men are less responsive to gonadotroph stimulation, and there are decreased numbers of Leydig cells in the testes. As men age, the pulsatile nature and amplitude of GnRH secretion decrease, consequently decreasing LH production [35].

The cutoff for diagnosing TD varies according to different sources, but the most recent guidelines as of 2018 recommend 300 ng/dl as the cutoff [36, 37]. It is recommended to measure total serum testosterone in the morning because of the diurnal pattern of testosterone levels. The highest level is reached in the early morning, and low values should be confirmed by a second assay [38]. Hypogonadism is usually diagnosed by a combination of low serum testosterone and clinical symptoms. Early symptoms of TD are fatigue, irritability, and decreased libido [39]. More severe and prolonged TD may result in regression of secondary sex characteristics, anemia, muscle wasting, osteoporosis, oligospermia, and abdominal adiposity [40]. Notable sexual symptoms include decreased libido, decreased sexual activity, decreased frequency of morning erections, and erectile dysfunction [41]. Psychological symptoms can include decreased energy, depressed mood, sleep disturbances, and poor concentration and memory [42].

As noted above, it is important to consider the sex hormone-binding globulin (SHBG), free testosterone, and possibly decreased sensitivity of AR when interpreting the variability between T levels and symptoms [20–23].

Testosterone Replacement Therapy

The goal of TRT is to restore the normal T levels of the individual without achieving supraphysiologic concentrations and subsequently improving the symptoms of hypogonadism [43]. It is best to use natural T, as opposed to synthetic androgens, since this allows for the whole range of physiologic effects to be achieved. There are many methods of preparation for T, such as oral (not FDA approved), intramuscular, transdermal, subdermal, buccal, and nasal agents. However, natural T is heavily absorbed by the intestine and metabolized by the liver before it can reach significant levels in the blood stream, so the oral route is not recommended for natural T due to low bioavailability [44]. All these routes of administration have various advantages and disadvantages.

TRT in hypogonadal men improves libido, erectile function, and overall sexual satisfaction [45]. TRT also improves bone mineral density, body composition, muscle mass and strength, mood, energy, quality of life, cognitive function, and anemia [46]. TRT has been shown to improve risk factors for CVD. In an analysis of multiple studies, individuals on TRT show significant reductions in serum total cholesterol (-0.4 to -0.23 mmol/l), LDL (-0.98 to 0.1 mmol/l), and triglycerides (-0.39 to -0.05 mmol/l), as well as an increase in HDL (-0.05 to 0.692 mmol/l) [47, 48]. These effects appear after 4 weeks and are maximal after 6–12 months [48]. TRT is also associated with a reduction in weight, BMI, and visceral fat [47]. Fat mass was decreased by 0.4 to 5.7 kg, on average [48]. Percent body fat was also significantly decreased after 90 days in men receiving testosterone gel (doses of 50 and 100 mg/day) compared to placebo ($P=0.0018$ and $P=0.0001$, respectively) [49]. The reduction was $-1.0\pm0.3\%$ in the 50 mg/day group and $-1.8\pm0.2\%$ in the 100 mg/day group [49]. This is important because obesity and hypogonadism exist in a vicious cycle. Obesity is a major cause of hypogonadism, and hypogonadism can lead to increased adiposity [9, 50]. TRT can also improve metabolic syndrome and diabetes by increasing insulin sensitivity which leads to better glycemic control and lower HbA1c [7]. Double-blind placebo-controlled studies showed that TRT reduced HbA1c by

approximately 0.8% by 18 months [47, 51] (see Fig. 1 for the multiple beneficial effects of testosterone replacement therapy in hypogonadal men).

Men who did not achieve therapeutic levels of T had higher rates of myocardial infarction, stroke, and death compared to men who achieved therapeutic levels of serum T. Also, these subtherapeutic men had similar rates of myocardial infarction and stroke as men who did not receive TRT [52]. Achieving physiologic levels of T can have a cardioprotective effect. Several studies have demonstrated reduced carotid intima media thickness in response to TRT, which is a marker of atherosclerosis [53]. In hypogonadal rats, TRT increased cardiac contractility, and cardiomyocytes displayed quicker relaxation [54, 55]. In men, TRT alleviated the risk of torsade's de pointes by decreasing the QT interval [56]. It is thought that T shortens the QT interval by upregulating K^+ currents and suppressing Ca^{2+} currents [57]. In men with coronary artery disease, T increased the time to exercise induced ST-segment depression on treadmill stress testing [58–60], possibly due to the vasodilatory and anti-ischemic effects of T [61]. Endothelin-1, a potent vasoconstrictor, was found to be increased in males with hypogonadism and lowered when treated with T [10, 62]. TRT is also associated with a decrease in proinflammatory cytokines such as interleukin-1β, which is thought to play a role in the development of atherosclerosis and coronary artery disease [63]. IL-1β decreases the β-adrenergic responsiveness of L-type Ca^{2+} channels and decreases expression of Ca^{2+} regulatory genes. IL-1β also increased expression of nitric oxide synthase in cardiac myocytes, which leads to lower energy production and myocardial contractility [64]. TRT in hypogonadal men shifted cytokine balance by downregulating inflammatory cytokines and upregulating anti-inflammatory cytokines like IL-10 [65]. These proinflammatory cytokines act on the hypothalamic-pituitary-gonadal axis and result in decreased T production in the testes, which can result in a negative feedback loop [66]. In patients with heart failure, TD is correlated with New York Heart Association (NYHA) class, functional exercise capacity, and worse clinical prognosis and mortality. TRT can have beneficial effects a number of these heart failure factors if the patient is hypogonadal [67]. In a meta-analysis of four studies, it was revealed that 35% of hypogonadal men with heart failure saw an improvement in NYHA functional class when on TRT [68].

Men on TRT do show an increase in overall prostate size, but this increase does not differ from men who are not on TRT. There is no link between increasing lower urinary tract symptoms and TRT, so there is not a contraindication for TRT in men with benign prostatic hypertrophy [69]. A

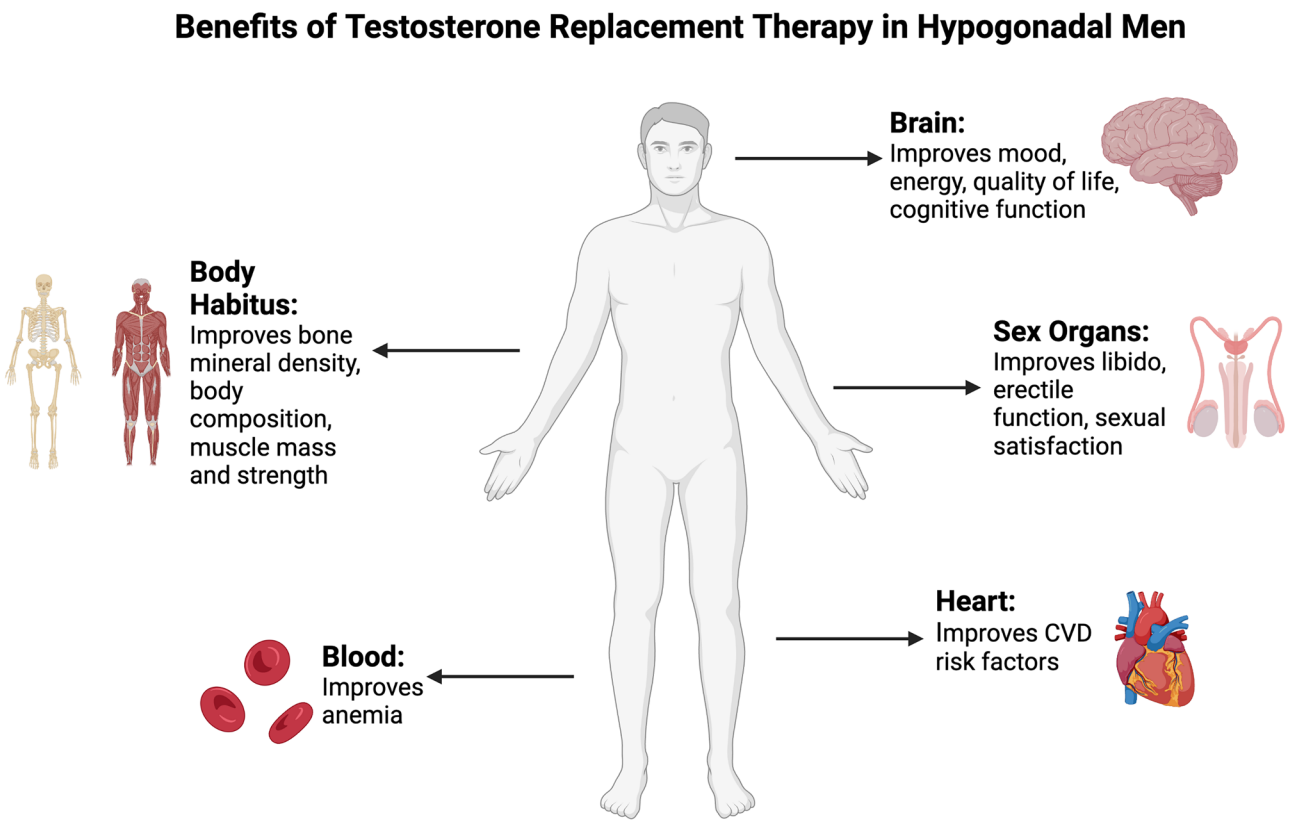

Fig. 1 Benefits of testosterone replacement therapy in hypogonadal men. Created with BioRender.com

relationship between serum testosterone levels and prostate cancer progression was first described in the 1940s [70]. Furthermore, in 1982, it was reported that men with metastatic prostate cancer given TRT had worse outcomes [71]. This has led to a prohibition in prescribing TRT to men with a history of prostate cancer or an increased risk for prostate cancer. The discovery of androgen deprivation as a treatment for prostate cancer was a significant finding, but misinterpretation of this work has led to inaccurate conclusions surrounding TRT and prostate cancer [72] The prostate cancer rate in TRT trials is only 1%, which is similar to the rates of detection in screening programs [73]. Several studies have failed to find a higher than expected risk of prostate cancer progression or reoccurrence in men who were previously treated with prostate cancer [72].

A common side effect of TRT is erythrocyte proliferation and resulting polycythemia [74]. Increased blood viscosity may predispose to ischemic sequelae. It is recommended that patients on TRT have CBC monitoring of hemoglobin prior to initiation, at 3 to 6 months, 12 months, and annually thereafter [33]. Therapeutic phlebotomies should be initiated at hemoglobin levels greater than 18 g/dl and monitored thereafter [75]. Hematocrit greater than 54% is a contraindication for TRT [7].

Conclusion

The Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) is a randomized, double-blind, placebo-controlled study with the goal of determining the safety of long-term TRT regarding major adverse cardiovascular events in middle-aged and older men with hypogonadism. TRAVERSE is the largest (5246 participants) and longest duration (up to 5 years) randomized study about the safety of TRT ever conducted. The patients either received daily transdermal 1.62% testosterone gel or matching placebo gel in metered-dose pumps. The average age of participants was 63.3 ± 7.9 years. 54.2% of the testosterone group and 55.2% of the placebo group had pre-existing cardiovascular disease. Median testosterone level at baseline was 227 ng/dl interquartile range 188–285) for the testosterone group and 227 ng/dl (interquartile range 188–258) for the placebo group. The average duration of treatments for the testosterone and placebo groups was 21.8 ± 14.2 and 21.6 ± 14.0 months, respectively. At 12 months, the average increase in serum testosterone in the treatment group was 148 ng/dl, compared to 14 ng/dl in the placebo group. The primary safety end point was the first occurrence of any component of major adverse cardiac events, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis [76]. The study was completed on January 19, 2023 [77••, 78]. The data showed that TRT was noninferior to placebo in incidence of major adverse cardiac effects [76]. Prostate cancer occurred in 0.5% patients in the testosterone group and 0.4% of patients in the placebo group ($P = 0.87$) [76]. Unexpectedly, the testosterone group has more cases of nonfatal arrhythmias warranting intervention (5.2% versus 3.3%, $P = 0.001$) [76]. Atrial fibrillation occurred in 3.5% of the testosterone group and 2.4% of the placebo group, although this is not a significant difference ($P = 0.02$). This is at odds with a cohort study which suggested decreased atrial fibrillation incidence with testosterone normalization [52]. Acute kidney injury occurred in 2.3% of the T group and 1.5% of the placebo group ($P = 0.04$) [76].These findings added to previous studies will facilitate a more informed consideration of potential benefits and risks regarding TRT in middle-aged and older hypogonadal men regarding the cardiovascular safety.

As with all therapies, the goal is to maximize the benefits and minimize the risks. This includes creating a standardized plan to monitor the patient's symptoms, side effects, hemoglobin, and testosterone levels [72]. A review of data clearly supports the cardiovascular safety of appropriately monitored testosterone therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Togun A, Sankar A, Karaca-Mandic P. FDA safety warnings and trends in testosterone marketing to physicians. 2022;28 **The FDA modification of testosterone labels in 2015 to indicate increased risk of stroke and heart attack still exists despite many studies indicating that there is not increased risk.**
2. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363:109–22.
3. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310:1829–36.
4. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF, Hoover RN. Increased Risk of non-fatal

myocardial infarction following testosterone therapy prescription in men. PLoS ONE. 2014;9:e85805.
5. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013;11:108.
6. Fundamental concepts regarding testosterone deficiency and treatment - clinicalkey. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S002561961630115X?scrollTo=%23hl0000873. Accessed 12 May 2023.
7. Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the heart. Methodist Debakey Cardiovasc J. 2017;13:68.
8. Gagliano-Jucá T, Basaria S. Trials of testosterone replacement reporting cardiovascular adverse events. Asian J Androl. 2018;20:131–7.
9. Kaur H, Werstuck GH. The effect of testosterone on cardiovascular disease and cardiovascular risk factors in men: a review of clinical and preclinical data. CJC Open. 2021;3:1238–48.
10. Gonzales JR, Goldstein I. Testosterone replacement and cardiovascular risk what do endocrinologists need to know? Cardiovascular Endocrinology & Metabolism. 2015;4:100–7.
11. Baillargeon J, Kuo Y-F, Westra JR, Urban RJ, Goodwin JS. Testosterone prescribing in the United States, 2002–2016. JAMA. 2018;320:200–2.
12. Klein CE. The hypothalamic-pituitary-gonadal axis. Holland-Frei Cancer Medicine. 6th edition. BC Decker, Hamilton (ON) 2003.
13. Wang Y, Chen F, Ye L, Zirkin B, Chen H. Steroidogenesis in Leydig cells: effects of aging and environmental factors. Reproduction. 2017;154:R111–22.
14. Aghazadeh Y, Zirkin BR, Papadopoulos V. Chapter Seven - Pharmacological regulation of the cholesterol transport machinery in steroidogenic cells of the testis. In: Litwack G, editor. Vitamins & Hormones. Academic Press; 2015. p. 189–227.
15. Handelsman DJ. Androgen physiology, pharmacology, use and misuse. Endotext. 2000 http://www.ncbi.nlm.nih.gov/books/NBK279000/. Accessed 11 May 2023.
16. Wilson JD. The role of 5alpha-reduction in steroid hormone physiology. Reprod Fertil Dev. 2001;13:673–8.
17. Simpson ER. Aromatase: biologic relevance of tissue-specific expression. Semin Reprod Med. 2004;22:11–23.
18. Quigley CA, Bellis AD, Marschke KB, El-Awady MK, Wilson EM, French FS. Androgen receptor defects: historical, clinical, and molecular perspectives*. Endocr Rev. 1995;16:271–321.
19. Prescott J, Coetzee GA. Molecular chaperones throughout the life cycle of the androgen receptor. Cancer Lett. 2006;231:12–9.
20. Panizzon MS, Bree K, Hsieh T-C, Hauger R, Xian H, Jacobson K, Lyons MJ, Franz CE. Genetic variation in the androgen receptor modifies the association between testosterone and vitality in middle-aged men. J Sex Med. 2020;17:2351–61.
21. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. 1994;22:3181–6.
22. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. Endocr Rev. 2017;38:302–24.
23. Ramasamy R, Golan R, Wilken N, Scovell JM, Lipshultz LI. Association of free testosterone with hypogonadal symptoms in men with near-normal total testosterone levels. Urology. 2015;86:287–90.
24. Nassar GN, Leslie SW. Physiology, testosterone. StatPearls: StatPearls Publishing, Treasure Island (FL); 2023.
25. Men and heart disease. In: Centers for Disease Control and Prevention. 2022 https://www.cdc.gov/heartdisease/men.htm. Accessed 11 May 2023.
26. Frančula-Zaninović S, Nola IA. Management of measurable variable cardiovascular disease' risk factors. Curr Cardiol Rev. 2018;14:153–63.
27. Er F, Michels G, Brandt MC, Khan I, Haase H, Eicks M, Lindner M, Hoppe UC. Impact of testosterone on cardiac L-type calcium channels and Ca2+ sparks: acute actions antagonize chronic effects. Cell Calcium. 2007;41:467–77.
28. Albrektsen G, Heuch I, Løchen M-L, Thelle DS, Wilsgaard T, Njølstad I, Bønaa KH. Lifelong gender gap in risk of incident myocardial infarction: the Tromsø study. JAMA Intern Med. 2016;176:1673–9.
29. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ. 2017;8:33.
30. Anaissie J, DeLay KJ, Wang W, Hatzichristodoulou G, Hellstrom WJ. Testosterone deficiency in adults and corresponding treatment patterns across the globe. Transl Androl Urol. 2017;6:183–91.
31. Mulligan T, Frick M, Zuraw Q, Stemhagen A, Mcwhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006;60:762–769.
32. Basaria S. Male hypogonadism. Lancet. 2014;383:1250–63.
33. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone therapy in men with hypogonadism: an endocrine society* clinical practice guideline. J Clin Endocrinol Metab. 2018;103:1715–44.
34. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. Int J Clin Pract. 2010;64:682–96.
35. Golan R, Scovell JM, Ramasamy R. Age-Related testosterone decline is due to waning of both testicular and hypothalamic-pituitary function. Aging Male. 2015;18:201–4.
36. Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proc (Bayl Univ Med Cent). 2014;27:321–4.
37. Testosterone deficiency guideline - American Urological Association. https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline. Accessed 9 Jun 2023.
38. Prevalence, diagnosis and treatment of hypogonadism in primary care practice » sexual medicine » BUMC. https://www.bumc.bu.edu/sexualmedicine/publications/prevalence-diagnosis-and-treatment-of-hypogonadism-in-primary-care-practice/. Accessed 18 May 2023.
39. Low testosterone: symptoms, diagnosis & treatment - Urology Care Foundation. https://www.urologyhealth.org/urology-a-z/l/low-testosterone. Accessed 1 Jun 2023.
40. Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: symptoms and treatment. J Adv Pharm Technol Res. 2010;1:297–301.
41. Kaufman J-M. Diagnosis of hypogonadism in ageing men. Rev Endocr Metab Disord. 2022;23:1139–50.
42. Diagnosis and evaluation of hypogonadism - ClinicalKey. https://www-clinicalkey-com.libux.utmb.edu/#!/content/playContent/1-s2.0-S0889852921001018?scrollTo=%23hl0000352. Accessed 18 May 2023.
43. Pharmacology of testosterone replacement therapy preparations - PMC. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5182226/. Accessed 24 May 2023.
44. Tsametis CP, Isidori AM. Testosterone replacement therapy: for whom, when and how? Metabolism. 2018;86:69–78.
45. Rastrelli G, Guaraldi F, Reismann Y, Sforza A, Isidori AM, Maggi M, Corona G. Testosterone replacement therapy for sexual symptoms. Sexual Medicine Reviews. 2019;7:464–75.
46. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag. 2009;5:427–48.

47. Hackett GI. Testosterone replacement therapy and mortality in older men. Drug Saf. 2016;39:117–30.
48. Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol. 2011;165:675–85.
49. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman the Testosterone Gel Study Group N. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men 1. J Clin Endocrinol Metab. 2000;85:2839–53.
50. Carrageta DF, Oliveira PF, Alves MG, Monteiro MP. Obesity and male hypogonadism: tales of a vicious cycle. Obes Rev. 2019;20:1148–58.
51. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, the BLAST Study Group. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. 2014;11:840–56.
52. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015;36:2706–15.
53. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism. https://doi.org/10.1177/1074248417691136
54. Golden KL, Marsh JD, Jiang Y, Moulden J. Acute actions of testosterone on contractile function of isolated rat ventricular myocytes. Eur J Endocrinol. 2005;152:479–83.
55. Eleawa SM, Sakr HF, Hussein AM, Assiri AS, Bayoumy NMK, Alkhateeb M. Effect of testosterone replacement therapy on cardiac performance and oxidative stress in orchidectomized rats. Acta Physiol (Oxf). 2013;209:136–47.
56. Salem J-E, Waintraub X, Courtillot C, et al. Hypogonadism as a reversible cause of Torsade de Pointes in men. Circulation. 2018;138:110–3.
57. Gutierrez G, Wamboldt R, Baranchuk A. The impact of testosterone on the QT interval: a systematic review. Curr Probl Cardiol. 2022;47: 100882.
58. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. Circulation. 2000;102:1906–11.
59. Webb CM, Adamson DL, de Zeigler D, Collins P. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. Am J Cardiol. 1999;83(437–439):A9.
60. Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, della Monica PL, Bonfigli B, Volpe M, Chierchia SL (1999) Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation 99:1666–1670.
61. Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, Channer KS. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart. 2004;90:871–6.
62. Kumanov P, Tomova A, Kirilov G. Testosterone replacement therapy in male hypogonadism is not associated with increase of endothelin-1 levels. Int J Androl. 2007;30:41–7.
63. Nettleship JE, Pugh PJ, Channer KS, Jones T, Jones RD. Inverse relationship between serum levels of interleukin-1beta and testosterone in men with stable coronary artery disease. Horm Metab Res. 2007;39:366–71.
64. Szekely Y, Arbel Y. A review of interleukin-1 in heart disease: where do we stand today? Cardiol Ther. 2018;7:25–44.
65. Mohamad N-V, Wong SK, Wan Hasan WN, Jolly JJ, Nur-Farhana MF, Ima-Nirwana S, Chin K-Y. The relationship between circulating testosterone and inflammatory cytokines in men. Aging Male. 2019;22:129–40.
66. Diaconu R, Donoiu I, Mirea O, Bălşeanu TA. Testosterone, cardiomyopathies, and heart failure: a narrative review. Asian J Androl. 2021;23:348–56.
67. Di Lodovico E, Facondo P, Delbarba A, Pezzaioli LC, Maffezzoni F, Cappelli C, Ferlin A. Testosterone, hypogonadism, and heart failure. Circulation: Heart Failure 2022;15:e008755.
68. Toma M, McAlister FA, Coglianese EE, Vidi V, Vasaiwala S, Bakal JA, Armstrong PW, Ezekowitz JA. Testosterone supplementation in heart failure. Circulation: Heart Failure 2012;5:315–321.
69. Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. Indian J Urol. 2014;30:2–7.
70. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22:232–40.
71. Fowler JE, Whitmore WF. Considerations for the use of testosterone with systemic chemotherapy in prostatic cancer. Cancer. 1982;49:1373–7.
72. Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone therapy in men with prostate cancer. Eur Urol. 2016;69:894–903.
73. Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006;7:363–9.
74. Jones SD Jr, Dukovac T, Sangkum P, Yafi FA, Hellstrom WJG. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. Sex Med Rev. 2015;3:101–12.
75. Van Buren NL, Hove AJ, French TA, Gorlin JB. Therapeutic phlebotomy for testosterone-induced polycythemia: a blood center's perspective. Am J Clin Pathol. 2020;154:33–7.
76. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med. 2023. https://doi.org/10.1056/NEJMoa2215025.
77.•• AbbVie. Testosterone replacement therapy for assessment of long-term vascular events and efficacy response in hypogonadal men (TRAVERSE) study. 2023. clinicaltrials.gov. **This is the largest and longest randomized control trial regarding testosterone replacement therapy and cardiovascular adverse events. The data reveals that TRT is noninferior to placebo regarding CV events.**
78. Bhasin S, Lincoff AM, Basaria S, et al. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: rationale and design of the TRAVERSE study. Am Heart J. 2022;245:41–50.