REVIEW

The effects of testosterone replacement therapy on the prostate: a clinical perspective [version 1; referees: 2 approved]

Saiful Miah1,2, Tharu Tharakan1, Kylie A Gallagher1, Taimur T Shah1,3, Mathias Winkler1, Channa N Jayasena4, Hashim U Ahmed1,3, Suks Minhas1

1Department of Urology, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, UK
2Division of Surgery and Interventional Science, University College London Medical School, 21 University Street, London, WC1E 6AU, UK
3Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, SW7 2AZ, UK
4Section of Investigative Medicine, Department of Medicine, Imperial College London, London, W12 0NN, UK

Abstract

Male hypogonadism is a clinical syndrome characterized by low testosterone and symptoms of androgen deficiency. Prostate cancer remains a significant health burden and cause of male mortality worldwide. The use of testosterone replacement therapy drugs is rising year-on-year for the treatment of androgen deficiency and has reached global proportions. As clinicians, we must be well versed and provide appropriate counseling for men prior to the commencement of testosterone replacement therapy. This review summarizes the current clinical and basic science evidence in relation to this commonly encountered clinical scenario. There is gathering evidence that suggests, from an oncological perspective, that it is safe to commence testosterone replacement therapy for men who have a combination of biochemically confirmed androgen deficiency and who have either had definitive treatment of their prostate cancer or no previous history of this disease. However, patients must be made aware and cautioned that there is a distinct lack of level 1 evidence. Calls for such studies have been made throughout the urological and andrological community to provide a definitive answer. For those with a diagnosis of prostate cancer that remains untreated, there is a sparsity of evidence and therefore clinicians are "pushing the limits" of safety when considering the commencement of testosterone replacement therapy.

Keywords

Prostate cancer, testosterone replacement therapy, late onset hypogonadism, androgen deprivation, andropause

Open Peer Review

Referee Status: ✔ ✔

Invited Referees

| 1 | 2 |
|---|---|
| version 1 published | ✔ | ✔ |

25 Feb 2019, 8(F1000 Faculty Rev):217 (https://doi.org/10.12688/f1000research.16497.1)

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 Ates Kadioğlu, University of Istanbul, School of Medicine, Turkey
2 Yaşar Pazir, University of Istanbul, Turkey
3 Larry I. Lipshultz, Baylor College of Medicine, USA

Any comments on the article can be found at the end of the article.
Corresponding author: Saiful Miah (saiful.miah@nhs.net)

Author roles: Miah S: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; Tharakan T: Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Gallagher KA: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Shah TT: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Winkler M: Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Jayasena CN: Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Ahmed HU: Supervision, Writing – Review & Editing; Minhas S: Conceptualization, Formal Analysis, Methodology, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2019 Miah S et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Miah S, Tharakan T, Gallagher KA et al. The effects of testosterone replacement therapy on the prostate: a clinical perspective [version 1; referees: 2 approved] F1000Research 2019, 8(F1000 Faculty Rev):217 (https://doi.org/10.12688/f1000research.16497.1)

First published: 25 Feb 2019, 8(F1000 Faculty Rev):217 (https://doi.org/10.12688/f1000research.16497.1)
Introduction
Male hypogonadism is a clinical syndrome attributed to androgen deficiency (AD). It can detrimentally affect multiple organ functions in addition to having detrimental effects on quality of life in men. Testosterone levels progressively decrease with age. After the age of 40 years, testosterone levels in men have been shown to decrease 1 to 2% per year. By the seventh decade, 35% of men have been shown to have lower testosterone levels than younger men. This has led to the emergence of a group of men older than age 65 years with hypogonadism with so-called “late-onset” hypogonadism (LOH) with its extensive symptom complex including obesity and loss of libido (Table 1).

Prostate cancer (PCa) remains a significant health burden and cause of male mortality. The National Cancer Institute has estimated that, in the US, over 3 million men are living with PCa. It was also estimated that an additional 164,690 cases would be diagnosed in the US during 2018 alone. The seminal and Nobel prize–winning study by Huggins and Hodges established the androgen hypothesis in that the growth and progression of PCa are directly related to male androgenic activity when withdrawing these hormones. However, nearly 80 years after this publication, there remains controversy and great debate on whether exogenous administration of testosterone will increase the risk of development or the progression of PCa. The urgent need for an answer to this is due in part to the sheer volume of the administration of testosterone replacement therapy (TRT), which is now one of the most widely prescribed medications in the US. The scientific community still seeks a definitive stance on the oncogenic safety profile of TRT in relation to PCa. In this review, we address the issue of whether there is an association between TRT and PCa by using evidence ranging from basic science to genetic and major epidemiological studies conducted on this topic.

Pathophysiology of androgen-driven prostate cancer
In 1941, Huggins and Hodges demonstrated that testosterone was an oncogenic driving hormone in PCa. In their study, acid phosphatase activity was elevated in serum specimens of 21 out of 47 PCa cases and 19 out of 25 cases with confirmed bone metastasis. Eight men who harbored skeletal metastasis then underwent castration. Their elevated acid phosphatase levels fell rapidly, indicating the androgen dependence of this oncological biomarker. The subsequent administration of testosterone to these men restored acid phosphatase to a level higher than pre-castration levels.

Owing to their extensive first-pass metabolism through the liver, oral preparations of testosterone are not widely used in TRT. Methods of replacement are administered predominantly by transdermal gel or intramuscular depot injection. Testosterone is metabolized to 5α-dihydrotestosterone (DHT), and both testosterone and 5α-DHT contribute to prostatic growth. There is abundant evidence that, within an in vitro environment, PCa cell lines are androgen-dependent in that they will undergo apoptosis and reduced cellular proliferation with the withdrawal of this hormone. For cell lines, androgens are critical for the development and maintenance of normal and cancer tissue, and the androgen receptor (AR) is the main therapeutic target for PCa. This phenomenon is further supported by in vivo studies where the administration of androgens creates a pro-tumorigenic environment in murine xenograft models, and the converse effect follows androgen suppression.

Androgen deprivation therapy (ADT) using gonadotrophin-releasing hormone (GnRH) super-agonists remains the cornerstone of the treatment of metastatic PCa. ADT for the majority of PCas will progress to androgen-independent disease. The development of resistance to apoptosis associated with androgen independence is one of the critical later stages of the molecular hallmarks of advanced PCa. Several mechanisms have been postulated to explain the transformation of ADT-responsive PCa to castrate-resistant PCa. These include overexpression of the AR, mutations in the AR, altered recruitment of transcription cofactors, and sustained intratumoral synthesis of DHT.

Androgen saturation theory
The androgen saturation theory proposes that the effects of testosterone on the prostate are limited by the capacity and concentration of prostate ARs. Therefore, testosterone above a given threshold level will have no effect on the prostate. In prostatic tissue, the AR becomes saturated at about 4 nmol/L (120 ng/dL) in vitro, corresponding to about 8 nmol/L (240 ng/dL) in vivo because of the presence of binding hormones. This model suggests why serum testosterone may appear unrelated to PCa risk in the general population and why testosterone administration in men with metastatic PCa causes rapid progression in castrated but not hormonally intact men. This is a significant shift of paradigm from the historical dogma that testosterone drives PCa.

Clinically, this theory was consolidated with the discovery that, although TRT increases serum testosterone levels, it did not correlate with intraprostatic testosterone levels on biopsy specimens of men on TRT. Furthermore, in-depth proteomic and genomic analysis of these histological specimens failed to
demonstrate an increased expression of PCa-related tissue biomarkers (AR, Ki-67, and CD34) or genes (AR, prostate-specific antigen [PSA], PAP2A, VEGF, NNX3, and CLU [Clusterin])23.

**Testosterone replacement therapy in men without a diagnosis of prostate cancer**

The majority of studies on TRT and PCa risk are limited by either insufficient power to determine this risk or their retrospective design (Table 2)24. In 2005, Calof et al.25 reported a meta-analysis of 19 studies, which included 651 men who received TRT, demonstrating that there was no statistically significant difference in PCa diagnoses among those who used testosterone25. Haider et al.26 reported on a multi-center prospective cohort study consisting of a total of 1023 hypogonadal men who received TRT. With a median follow-up of 5 years, the incidence of PCa was lower in TRT-treated populations than accepted incidence rates from large population-based studies with long-term follow-up24,26. The limitations of this study include a younger cohort of patients with a mean age of only 58 years, thus making it challenging to draw comparisons with large screening trials such as Prostate, Lung, Colorectal, and Ovarian (PLCO) and the European Randomized Study of Screening for Prostate Cancer27. For those men who harbor high-grade prostatic intraepithelial neoplasia (PIN), it has been shown that with short-term follow-up there is no greater risk of an increase of their PSA or PCa compared to those men without PIN28.

**Contemporary epidemiological studies**

A recently published article by Loeb et al.29 reported a large nested case-control study which included over 38,000 and 192,000 men with diagnosed PCa or free from the disease, respectively. This study demonstrated that there was no overall increase in risk of PCa in those men who received TRT (odds ratio [OR] 1.03, 95% confidence interval [CI] 0.90–1.17). Once the breakdown of disease subtype was analyzed between favorable (T1–T2, PSA <10 ng/mL, Gleason score [GS] ≤6, not N1, no M1) and aggressive (local high risk, T1–T2, GS of 8–10, PSA 20–50 ng/mL, no N1, no M1) disease, locally advanced (T3, PSA >50 ng/mL, not N1, not M1), regionally metastatic (T4, PSA 50–100 ng/mL, N1, no M1), and metastatic (metastases on bone imaging or PSA >100 ng/mL) results demonstrated the clinical benefits of commencing TRT. TRT demonstrated an early increase in favorable-risk PCa (OR 1.35, 95% CI 1.16–1.56), which was balanced with a finding that those men on TRT significantly lowered their risk of harboring aggressive PCas (OR 0.50, 95% CI 0.37–0.67). The vast majority of favorable PCa fell within the spectrum of clinically insignificant PCa29. There has been a recent shift and drive to change the nomenclature associated with PCa, including calls to drop the label “cancer” with certain favorable-risk PCa30. Well-characterized pure Gleason grade 3 disease fails to clearly show both clinical and molecular hallmarks that are expected of a cancer. Hence, a strategy that decreases the incidence of aggressive PCa at the expense of its favorable-risk counterpart would warrant further investigation and would be welcomed if robustly proven.

**Testosterone replacement therapy with treated prostate cancer**

There is now gathering evidence that men who have had their PCa treated by radical prostatectomy (RP) and external beam radiotherapy with curative intent are potentially safe to have TRT administered. However, again, these studies have inherent limitations, including the limited number of patients, the lack of long-term follow-up, and the fact that the study was designed to be a retrospective case series.

Kaufman and Graydon reported on seven men who underwent RP and who then were placed on TRT for biochemically confirmed hypogonadism31. On follow-up of these surgically treated men, no one was found to have either biochemical or clinical recurrence of their malignancy31. Khera et al.32 reported

| Authors         | Year | Study format          | Number on testosterone replacement therapy (TRT) | Conclusions                                                                 |
|-----------------|------|-----------------------|-------------------------------------------------|-----------------------------------------------------------------------------|
| Loeb et al.29   | 2017 | Nested case-control   | 1,662                                           | No overall increase in risk of prostate cancer (PCa). Early increase in the risk of favorable cancer (odds ratio [OR] 1.03, 95% confidence interval [CI] 0.90–1.17) and decrease in the risk of aggressive PCa (OR 0.50, 95% CI 0.37–0.67). |
| Haider et al.26 | 2015 | Prospective cohort (multi-center) | 1,023                                        | Lower incidence of PCa in TRT-treated populations                             |
| Eisenberg et al.28 | 2015 | Retrospective observational | 247                                         | There was no change in cancer risk overall, or PCa risk specifically, for men older than 40 years using long-term TRT. |
| Feneley et al.34 | 2012 | Prospective cohort (single-center) | 1,365                                         | Incidence of PCa during long-term TRT was equivalent to that of the general population. |
| Calof et al.25  | 2005 | Meta-analysis          | 651                                             | No statistically significant difference in PCa diagnoses among TRT users.    |
| Rhoden and Morgentaler31 | 2003 | Prospective cohort (single-center) | 75                                              | After 1 year of TRT, men with prostatic intraepithelial neoplasia (PIN) do not have a greater increase in prostate-specific antigen or a significantly increased risk of cancer than men without PIN. |
on a significantly larger cohort of men (n = 57) who underwent RP with confirmed negative surgical margins and subsequently commenced on TRT. With an average follow-up of 13 months (range of 1–99 months), no men in their study demonstrated biochemical recurrence of their cancer with their regular PSA surveillance. Similarly, for those men who opted to undergo external beam radiotherapy for their PCa and then commenced on TRT, Pastuszak et al. concluded that there was only a minor increase in serum PSA and a low rate of biochemical recurrence in their multi-center series of 98 men. The authors also commented that their 6.1% biochemical recurrence was lower than previously reported rates for radiation therapy, suggesting that TRT does not lead to biochemical failure in those men who received radical radiotherapy for their PCa.

Testosterone replacement therapy with untreated prostate cancer

A recent systematic review by Kaplan et al. highlighted the caution required when commencing TRT for men undergoing active surveillance (AS) or watchful waiting of their PCa as this is “pushing the limits of safety”. This conclusion was based primarily on the sparsity of evidence in this cohort of men with very minimal reports in comparison with those with no diagnosis or treated PCa. Kacker et al. recently reported their retrospective study in 28 men on AS for their PCa who commenced TRT for AD in comparison with 96 men in the untreated AD arm. The authors reported that biopsy progression rates were similar between these two groups over a 3-year follow-up period and appear unaffacted by TRT.

Non-oncological consequences of androgen deficiency

The metabolic syndrome (MetS) was first described in 1923 by Kylin. Later, Reaven coined the term “Syndrome X”, which is a constellation of insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol, and increased very-low-density lipoprotein and triglyceride to further define MetS. Owing to its associated risk of cardiovascular disease, MetS has been proposed as the main threat to public health in the 21st century. There are several definitions of MetS; however, the primary emphasis is on central obesity (Table 3), and the estimated prevalence of this among males in the US is 34.5%.

There is a strong inverse relationship with testosterone and body fat in men, and numerous epidemiological studies show the increase of MetS with declining testosterone levels. The central fat seen with abdominal obesity has high aromatase activity converting testosterone to estradiol. Furthermore, testosterone promotes lipolysis and inhibits adipocyte development.

About 50% of men with diagnosed PCa will be exposed to ADT at some stage of their disease. Again, the clinical adverse effects of low testosterone due to ADT are well reported and have a negative effect on quality of life. ADT in those with PCa has been linked to a metabolic-type syndrome of insulin insensitivity with its associated central obesity and decreased muscle mass.

Numerous interventional studies have shown that TRT in hypogonadal men with MetS has beneficial effects on central adiposity, insulin resistance, and glycemic control. In addition, TRT has shown improvements in well-established cardiovascular risk factors by lowering elevated blood pressure, triglyceride levels, and cholesterol. TRT has also been shown, in a prospective manner, to address the detrimental sexual dysfunction associated with LOH. The administration or TRT has been shown to result in a significant improvement in the various aspects of sexual function, including sexual desire, intercourse satisfaction, and overall satisfaction. Similarly, TRT has demonstrated significant improvement in depressive symptoms in those who received treatment within the setting of a randomized trial.

Commercial caution

TRT drugs have been a phenomenal commercial success and their pharmaceutical sales are rising year-on-year. The off-label indications have led to an exponential increase in the prescription of TRT in the US, and commercial marketing efforts are potentially linked to prescriber habits. This increased commercialism had included the use of TRT without the clinical or biochemical confirmation of hypogonadism, and there are calls to limit overtreatment with the application of strict diagnostic criteria of LOH. Alarmingly, there has been a fourfold increase in the use TRT in the younger cohort of men (18–45 years) in the US. This has potential clinical implications—not the least of which is the potential detrimental effect on fertility in this age group—that

| Central abdominal obesity waist circumference of at least 94 cm in Europids and of more than 90 cm in Asians AND |
|---------------------------------------------------------------|
| elevated triglycerides ≥1.7 mmol/L (≥150 mg/dL)               |
| reduced high-density lipoprotein cholesterol <1.03 mmol/L (<40 mg/dL) |
| elevated systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg (or treatment) |
| dysglycemia (raised fasting plasma glucose, fasting blood glucose ≥5.6 mmol/L [≥100 mg/dL]) (or type 2 diabetes mellitus) |
may not manifest until after several decades. This increased use in younger men would require future focused studies assessing the long-term oncological sequelae of early TRT use. Crucially, the potential oncological manifestations of TRT use in younger men may not reveal themselves for several decades.

Testosterone dependence has also been identified\(^5\). The cessation of TRT ultimately will result in the restoration of baseline serum testosterone levels; however, these men may feel markedly symptomatic and seek additional testosterone while waiting for normal levels to be achieved\(^5\). The current European Association of Urology guidelines on male hypogonadism advocate the use of TRT, including in those adult men with consistent and preferably multiple signs and symptoms of hypogonadism and a low testosterone following unsuccessful treatment of obesity and comorbidities.

Conclusions

With the increased use of TRT for the treatment of AD, it is essential that the clinician be well versed in its potential oncological implications. At present, there is no definitive evidence that administration of exogenous testosterone will increase the incidence of PCa. The absence of a large randomized clinical trial to address this topic is starkly obvious; such a study is vital before we can confidently counsel men who express interest in or harbor a clinical need for TRT. At best, we can provide these men only sub–level I evidence of TRT in relation to PCa, high-lighting the ambiguity and dearth of high-quality studies. In our clinical practice, when prescribing TRT, we make it paramount that patients be made aware that, although there may be a significant improvement in the signs and symptoms of LOH, the unlikely risk of developing a significant de novo or recurrence of their treated PCa as a direct result of pharmacological intervention is currently based on less-than-optimal data. When we are faced with those men with untreated PCa or on AS, we avoid TRT at present. However, we eagerly await further evidence that would suggest otherwise.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. McBride JA, Carson CC 3rd, Coward RM: Testosterone deficiency in the aging male. Ther Adv Urol. 2016; 8(1): 47–60. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
2. Harman SM, Metter EJ, Tobin JD, et al.: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging, J Clin Endocrinol Metab. 2001; 86(2): 724–31. Published Abstract | Publisher Full Text
3. Kaufman JM, Vermeulen A: The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev. 2005; 26(6): 833–76. Published Abstract | Publisher Full Text
4. Wu FC, Tajar A, Pye SR, et al.: Hypothalamic-pituitary-testicular axis dysfunctions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008; 93(7): 2737–45. Published Abstract | Publisher Full Text
5. Vermeulen A, Kaufman JM: Ageing of the hypothalamo-pituitary-testicular axis in men. Horm Res. 1995; 43(1–3): 25–8. Published Abstract | Publisher Full Text
6. Noone AH, Krapcho N, Miller M, et al.: SEER Cancer Statistics Review, 1975-2015. National cancer institute. 2018. Reference Source
7. Huggins C, Hodges CV: The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. Cancer Res. 1941; 1(4): 293–97. Reference Source
8. Morgentaler A: Testosterone Therapy Can be Given to Men with No Concern that it will Promote Prostate Cancer Development or Progression: Pro. J Urol. 2016; 196(4): 985–8. Published Abstract | Publisher Full Text | F1000 Recommendation
9. Gleaves ME, Klotz L: Testosterone Therapy Can be Given to Men with No Concern that it will Promote Prostate Cancer Development or Progression: Con. J Urol. 2016; 196(4): 985–8. Published Abstract | Publisher Full Text | F1000 Recommendation
10. Busnelli A, Somigliana E, Vercellin P: ‘Forever Young’-Testosterone replacement therapy: a blockbuster drug despite flabby evidence and broken promises. Hum Reprod. 2017; 32(4): 719–24. Published Abstract | Publisher Full Text
11. Nelson WG: Commentary on Huggins and Hodges: “Studies on Prostatic Cancer”. Cancer Res. 2016; 76(2): 186–7. Published Abstract | Publisher Full Text | F1000 Recommendation
12. Shoskes JJ, Wilson MK, Spinner ML: Pharmacology of testosterone replacement therapy preparations. Transl Androl Urol. 2016; 5(6): 834–43. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
13. Marchiani S, Tamburino L, Nesi G, et al.: Androgen-responsive and - unresponsive prostate cancer cell lines respond differently to stimuli inducing neuroendocrine differentiation. Int J Androl. 2010; 33(6): 784–93. Published Abstract | Publisher Full Text
14. Kyprianou N, English HF, Isaacs JT: ‘Forever Young’-Testosterone replacement therapy in men with prostate cancer: scientific and ethical considerations. J Urol. 2016; 195(1 Suppl): S26–33. Published Abstract | Publisher Full Text
15. Chang KH, Ercole CE, Sharifi N: Androgen metabolism in prostate cancer: from molecular mechanisms to clinical consequences. Br J Cancer. 2014; 111(7): 1249–54. Published Abstract | Publisher Full Text | Free Full Text
16. Arnold JT, Isaacs JT: Mechanisms involved in the progression of androgen-independent prostate cancers: it is not only the cancer cell’s fault. Endocr Relat Cancer. 2002; 9(1): 61–73. Published Abstract | Publisher Full Text
17. Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–74. Published Abstract | Publisher Full Text | F1000 Recommendation
18. Chang KH, Ercole CE, Sharifi N: Androgen metabolism in prostate cancer: from molecular mechanisms to clinical consequences. Br J Cancer. 2014; 111(7): 1249–54. Published Abstract | Publisher Full Text | Free Full Text
19. Morgentaler A: Testosterone therapy in men with prostate cancer: scientific and ethical considerations, J Urol. 2013; 189(1 Suppl): S26–33. Published Abstract | Publisher Full Text
20. Traish AM, Williams DF, Hoffman ND, et al.: Validation of the exchange assay for the measurement of androgen receptors in human and dog prostates. Prog Clin Biol Res. 1988; 256: 145–60. Published Abstract
21. Traish AM, Muller RE, Wolitz HJ: A new procedure for the quantitation of nuclear and cytoplasmic androgen receptors. J Biol Chem. 1981; 256(23): 12028–33. Published Abstract
22. Traish AM, Muller RE, Wolitz HJ: A new procedure for the quantitation of nuclear and cytoplasmic androgen receptors. J Biol Chem. 1981; 256(23): 12028–33. Published Abstract
23. Marks LS, Mazer NA, Mostaghel E, et al.: Effect of testosterone replacement...
therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA. 2006; 296(19): 2301–61. PubMed Abstract | Publisher Full Text | F1000 Recommendation

24. Michaud JE, Billups KL, Parin AW. Testosterone and prostate cancer: an evidence-based review of pathogenesis and oncologic risk. Ther Adv Urol. 2015; 7(6): 379–87. PubMed Abstract | Publisher Full Text | Free Full Text

25. Caod OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005; 60(11): 1451–7. PubMed Abstract | Publisher Full Text

26. Heider A, Zitzmann M, Doros G, et al. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. J Urol. 2015; 193(1): 80–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation

27. Butler P, Scowell JM, Ramaoy R, et al. Words of Wisdom: Re: Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. Eur Urol. 2015; 67(6): 1186–7. PubMed Abstract | Publisher Full Text

28. Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol. 2003; 170(6 Pt 1): 2348–51. PubMed Abstract | Publisher Full Text

29. Loeb S, Folkovoy J, Damber JE, et al. Testosterone Replacement Therapy and Risk of Favorable and Aggressive Prostate Cancer. J Clin Oncol. 2017; 35(13): 1430–6. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

30. Miah S, Ahmed HU, Freeman A, et al. Does true Gleason pattern 3 merit its cancer descriptor? Nat Rev Urol. 2016; 13(9): 541–8. PubMed Abstract | Publisher Full Text

31. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol. 2004; 172(3): 920–2. PubMed Abstract | Publisher Full Text

32. Khena M, Grober ED, Najar B, et al. Testosterone replacement therapy following radical prostatectomy. J Sex Med. 2009; 6(4): 1165–70. PubMed Abstract | Publisher Full Text

33. Eisenberg ML, Li S, Betts P, et al. Testosterone therapy and cancer risk. BJU Int. 2015; 116(2): 317–21. PubMed Abstract | Publisher Full Text | F1000 Recommendation

34. Fenley MR, Carruthers M. Is testosterone treatment good for the prostate? Study of safety during long-term treatment. J Sex Med. 2012; 9(8): 2138–49. PubMed Abstract | Publisher Full Text

35. Pastuszak AW, Krhanna A, Badhikasa N, et al. Testosterone Therapy after Radiation Therapy for Low, Intermediate and High Risk Prostate Cancer. J Urol. 2015; 194(5): 1271–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation

36. Kaplan AL, Hu JC, Morgenstern A, et al. Testosterone Therapy in Men With Prostate Cancer. Eur Urol. 2016; 69(5): 894–903. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

37. Kacker R, Huitt M, San Francisco IF, et al. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. Asian J Androl. 2016; 18(1): 16–20. PubMed Abstract | Publisher Full Text | Free Full Text

38. Reaven GM: Role of insulin resistance in human disease (syndrome X): an expanded definition. Ann Rev Med. 1993; 44: 121–31. PubMed Abstract | Publisher Full Text

39. Taskinen MR: Is metabolic syndrome the main threat to human health in the twenty-first century? Antioxidant Theorbi Molec. 2007; 27(11): 2275. PubMed Abstract | Publisher Full Text

40. Ford ES: Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care. 2005; 28(11): 2745–50. PubMed Abstract | Publisher Full Text

41. Alberti KG, Zimmet P, Shaw J: Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23(5): 469–80. PubMed Abstract | Publisher Full Text

42. Kapoor D, Malkin CJ, Chaners KS, et al. Androgen, insulin resistance and vascular disease in men. Clin Endocrinol (Oxf). 2005; 63(3): 239–50. PubMed Abstract | Publisher Full Text

43. Salam R, Khairelmayum AS, Keisam R. Testosterone and metabolic syndrome: the link. Indian J Endocrinol Metab. 2012; 16 Suppl 1: S12–9. PubMed Abstract | Publisher Full Text | Free Full Text

44. Gunner C, Gulumhusein A, Rosario DJ: The modern role of androgen deprivation therapy in the management of localised and locally advanced prostate cancer. J Clin Urol. 2016; 9(2): 24–9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

45. Nguyen PL, Alibba SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015; 67(5): 825–39. PubMed Abstract | Publisher Full Text | F1000 Recommendation

46. Herr HW, O’Sullivan M: Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. J Urol. 2000; 163(6): 1743–6. PubMed Abstract | Publisher Full Text

47. Kapoor D, Goodwin E, Chaners KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2006; 154(6): 899–906. PubMed Abstract | Publisher Full Text

48. Moon D, Park MG, Lee SW, et al. The efficacy and safety of testosterone undecanoate (Nebido®) in testosterone deficiency syndrome in Korean: a multicenter prospective study. J Sex Med. 2010; 7(6): 2253–66. PubMed Abstract | Publisher Full Text

49. Gilroy EJ, Tishova YA, Makhlaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med. 2010; 7(7): 2572–82. PubMed Abstract | Publisher Full Text

50. Bandari J, Ayash OM, Emery SL, et al. Marketing and Testosterone Treatment in the USA: A Systematic Review. Eur Urol Focus. 2017; 3(4–5): 395–402. PubMed Abstract | Publisher Full Text

51. Rao PK, Boulet SL, Mehta A, et al. Trends in Testosterone Replacement Therapy Use from 2003 to 2013 among Reproductive-Age Men in the United States. J Urol. 2017; 197(4): 1121–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation

52. Kim ED, Cossnow L, Bar-Chama N, et al. The treatment of hypogonadism in men of reproductive age. Ferti Steril. 2013; 99(3): 718–24. PubMed Abstract | Publisher Full Text | F1000 Recommendation
Open Peer Review

Current Referee Status: ✔ ✔

Editorial Note on the Review Process
F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 Larry I. Lipshultz Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, 77030, USA
   Competing Interests: No competing interests were disclosed.

2 Ates Kadioğlu Yaşar Pazır Section of Andrology, Department of Urology, University of Istanbul, School of Medicine, Istanbul, Turkey; Department of Urology, University of Istanbul, Istanbul, Turkey
   Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com