CURRENT ISSUES AND PROMISING APPROACHES IN TESTOSTERONE DEPLETION IN DIABETES

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Abstract

The testosterone levels of people with type 2 diabetes are lower than those of healthy young males. The hypothalamic-pituitary-gonad axis may fail in just a fraction of these individuals, resulting in typical hypogonadism. The cutoff threshold for blood testosterone in males without apparent hypothalamic-pituitary-gonadal axis disease is only a contested matter. Physical syndrome, hyperglycemia, and an increased risk of cardiovascular disease may be caused by both intrinsic and extrinsic factors interacting with the hypothalamic-pituitary-gonadal axis as well as glucose resistance and low-grade inflammation. There is still a need for additional studies to understand whether low blood testosterone levels are directly responsible for the development of unfavorable clinical outcomes, or whether they act as a mediating or moderating factor. At this time, there is no reliable information from randomized clinical studies on the effects of testosterone replacement therapy on significant clinical outcomes. Type 2 diabetics, for example, may have a higher risk of side effects from testosterone treatment than the general population.

Low blood testosterone levels in individuals with type 2 diabetes have been linked to increased cardiovascular risk factors, metabolic syndrome, as well as worsening clinical outcomes.

Keywords: Type 2 diabetes, Low Testosterone, Hypothalamic-pituitary-gonad axis, Glucose intolerance, Metabolic syndrome, Clinical studies.

Introduction

Nearly 90% of people with diabetes have type 2 diabetes, which is characterized by elevated blood sugar, insulin resistance, and also insulin deficiency. IDF estimates that by 2040, 642 million people will develop diabetes as a result of population growth, aging, physical inactivity, and even an elevation in obesity prevalence. There are now 415 million people with diabetes around the globe. Many medical disorders and medications may lead to diabetes. These include hypoandrogenism, glucocorticoids, thiazides, and statins [1–4]. Among anabolic steroids, testosterone is the most important for the male sex. As well as stimulating the development of primary sexual characteristics in men (such as the penis, testes, and prostate), testosterone also promotes the formation of secondary sexual characteristics in men. Testosterone has an important function in bone health and bone density preservation [5,6]. As a result of reduced testosterone levels, men may have erectile dysfunction, lower urinary tract symptoms, and inflammatory disorders, as well as higher cardiovascular risk factors [7–9]. Similarly, testosterone supplementation may improve glycemic control, urinary and sexual functioning, voiding symptoms, and life quality [10–15]. Increased lean body mass, reduced abdominal fat mass, lower total cholesterol, and better glycemic control have all been linked to a lower risk of heart disease in older men who maintain testosterone levels [8]. Insulin resistance and a higher likelihood of developing type 2 diabetes have been associated with reduced testosterone (TT) levels (17, 18–21). moreover, testosterone supplementation has been found in short-term trials in males to increase insulin sensitivity (22-25).

DETERMINATION OF LOW TESTOSTERONE LEVELS

Physicians have a difficult task when attempting to determine the lowest acceptable amount of serum testosterone. Firstly, it is not known what amount of testosterone in the general population causes unfavorable clinical effects. There have also been reports of significant differences in the standard ranges for blood testosterone levels(26). The testosterone reference ranges have

traditionally been generated from conventional samples or individuals in a hospital or clinic.20 These methods are hampered by the fact that people who seek medical attention are more probable to have an illness than those who do not seek treatment. As a result, for the time being, the majority of population-based studies can use the lower limit of the normal range for early age Caucasian men, which ranges from 8.7 to 12.7 nmol/L, as the cutoff point16,21. However, interethnic differences do exist due to various mechanisms, that would be discussed in the following review. (26-29).

Total, Free, and Protein-Bound Testosterone in Serum

Only the Leydig cells of the testes produce and release testosterone into the bloodstream in males. The majority of it is incorporated into plasma proteins. The serum includes 0.5–3.0 percentage unbound testosterone, 30–44 percentage SHBG-bound testosterone, and 54–68 percentage albumin-bound testosterone (30,31). (30,31). The amount of free and albumin-bound testosterone that's also accessible for cells is known as "bioavailable testosterone," although because binding of testosterone to albumin is non-specific and consequently not tight. Since a major percentage of circulating testosterone is firmly bound with SHBG, alterations in SHBG concentration may impact complete blood testosterone levels despite altering unbound or bioavailable testosterone. Lists factors that alter serum SHBG levels without changing testosterone levels are presented. Serum total and free testosterone were compared to see which was more accurate and useful for researching the effects of testosterone. The outcomes were not uniform. Serum total and free testosterone levels were shown to be significantly linked to clinical outcomes in some studies, but in others, just the free testosterone level or the total serum testosterone level was found to be significantly linked.(32,33)

Epidemiological studies of testosterone and type 2 diabetes/metabolic syndrome

Diabetic men's serum total testosterone levels was shown to be lower in population studies than that in nondiabetic controls. Total testosterone levels in diabetic males were 2.66 nmol/l lower than those in nondiabetic men, according to a review of 20 cross-sectional investigations that included 2,900 men (850 of whom had T2D) (P 0.001). When age, BMI, and waist-hip ratio were taken into account, the difference between diabetic and nondiabetic males was reduced, although remained significant, to 1.61 nmol/l (nmol/l) (P 14 0.001). The fat tissue in our bodies

was not taken into consideration in these studies, which merely employed anthropometric measures as a basis. Since there was no reliable data on free testosterone levels, we couldn't say for sure how much of the low total testosterone was due to SHBG deficiency. Tissue androgenization may be assessed using either free testosterone levels (which can be measured or estimated), as well as total testosterone levels, which have been the subject of other discussions here in this article. Inside the National Health and Nutrition Survey III cross-sectional investigation, total testosterone levels were significantly lower in men with T2D than in non-diabetic controls (1.4 nmol/l) after adjusting for BMI and WHR. Type 2 diabetes risk was 4.2 times greater among men within the low quartile of cFT (computational unbound testosterone) (P 14 0.04). Cross-sectional studies of men having type 2 diabetes are becoming increasingly common.580 Australian men 65 years of age with diabetes had a BMI of 30 kg/m2 in the largest study. It was found that only 43 percent and 57 percent of the adult, reproductively healthy men studied had normal testosterone assay values. 40% of males with a BMI under 25 kg/m2 had low testosterone, despite the fact that testosterone levels in this sample were adversely linked with both age and BMI. Two smaller studies conducted in the UK [38] and the USA [39] found that men with Type 2 Diabetes (T2D) were much more likely to have lower testosterone levels. Aging and obesity have not been studied as possible factors in the high frequency of low testosterone in these studies. Low total testosterone levels were also shown to be associated with metabolic syndrome (MetS) in three cross-sectional studies [40,41]. Only one of three studies indicated a link between MetS and testosterone-free testosterone. Study after study has looked at the link between low testosterone levels and diabetes [42,44]. The number of new cases of T2D at the end of an 8–11-year study varied from 26 to 57, regardless of the fact that 300–1700 men were involved. In two investigations, total testosterone and unbound testosterone were potential risk factors for T2D even after adjusting the initial BMI or WHR and insulin-resistant indices. Metabolic syndrome (MetS) has also been linked to low testosterone levels. Once obesity but also insulin resistance was taken into consideration, the negative relationship between free testosterone levels and Metabolic Syndrome was no longer apparent [44,45].

Testosterone replacement therapy

Study participants with hypogonadism were asked to lower fasting glucose, serum insulin, and triglyceride levels in order to improve their health. No substantial change was seen in

CVD(54).sMedicare data from the United States showed any higher risk of MI after testosterone injections, and testosterone seemed to be advantageous to those at higher risk of a cardiovascular event. (55). There have been just a few clinical studies that have been published so far, and they have been modest, brief, and employed pharmacological rather than physiological testosterone doses(47,48). It will be necessary to conduct a thorough phenotyping, a big sample size, and lengthy follow-up duration to evaluate testosterone replacement therapy's risks and advantages.

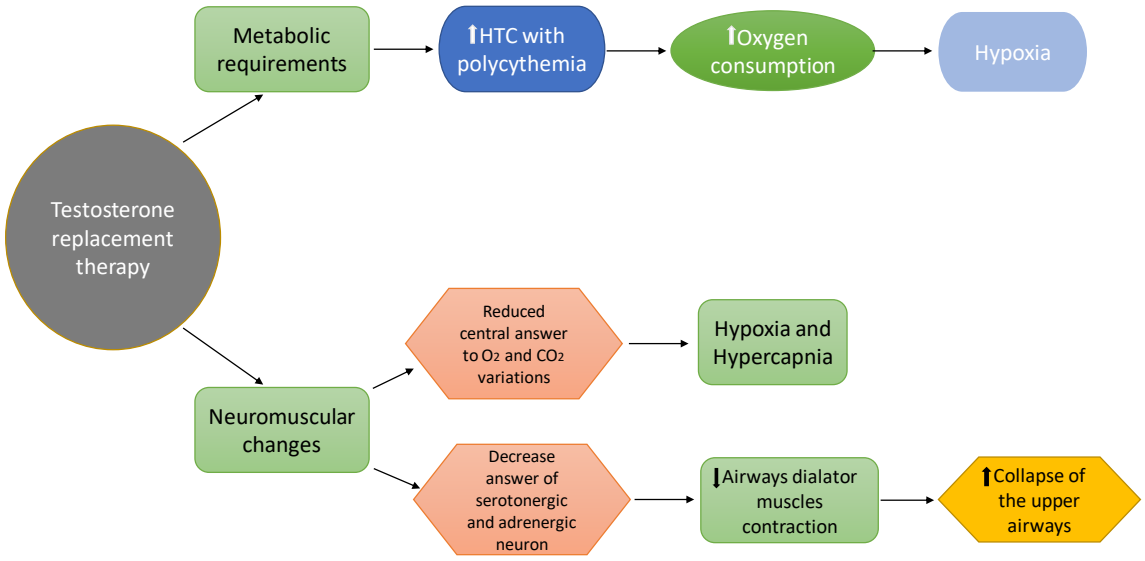

Figure :1 Schematic diagram of Testosterone replacement therapy

Note: The diagrams used in this review article have not been published in any journal and were created originally and innovatively using subject knowledge and Microsoft PowerPoint.

Depending on these experimental results, clinical studies assessing the impact of testosterone treatment on hypogonadal males were equivocal. Patients were administered either a 60-mg transdermal testosterone gel or even a placebo every day for the 12-month duration of the study, which reduced cardiovascular risk in men with type 2 diabetes and/or MES who showed evidence of androgen deficiency. The projected rise in HbA1c (a secondary aim) did not occur

since most participants had already been well-treated for type 2 diabetes (HbA1c 6.5%) and the impact was challenged by the permissible pharmaceutical changes for ethical reasons (47). Research on males with type 2 diabetes who are hypogonadal is thus needed. To evaluate whether testosterone gel or placebo may improve endurance and stair climbing skills in older men, the Testosterone in Elderly Men experiment included 209 participants. The data and safety protective measures ended the research in 2009 only three months after the last patient was recruited due to substantial cardiovascular effects in the investigation's treatment group. Active therapy patients had 23 myocardial infarctions, whereas patients in the placebo group had 5 myocardial infarctions (48,49). According to a study published in 2012, men in their 40s who seemed to have low testosterone or other health conditions were found to have decreased mortality rates if they received testosterone treatment (50). A European study of 64 diabetic men with low testosterone found a reduction in mortality with this medication over the same period (51). Only mortality, heart attack, and ischemic stroke risk were raised among veterans who had coronary angiography and low serum testosterone levels who received testosterone treatment, Based on studies presented in the Journal of the American Medical Association, it has been claimed in 2013. During the preceding 90 days, equally older and younger men who had been on testosterone therapy had a twofold and threefold rise in the risk of myocardial infarction (MI) (52,53). That's why FDA decided to reassess testosterone treatment's cardiovascular safety in January 2014. Due to pre-existing findings of venous bleeding unrelated to polycythemia with testosterone users, the FDA mandated in June 2014 that all testosterone preparations have an extensive warning regarding the risk of blood clots in the veins. It has been established that a testosterone substitute/placebo is effective.

CONCLUSION

It has been shown that decreased blood testosterone levels may cause Diabetes is connected to insulin resistance, which causes obesity, cardiovascular disease, and inflammation. Men suffering from type 2 diabetes and their testosterone levels who are asymptomatic should not be checked at this time since a causal link between low testosterone and poor clinical outcomes cannot yet be proven. Type 2 diabetes is quite common, and additional research is needed to determine if low testosterone is producing negative clinical results, or if it is just a reflection of bad health risk factors.

ACKNOWLEDGMENT

The Authors like to thank The JSS Academy of Higher Education and Research (JSS AHER), Jss College of Pharmacy, Ooty, Tamilnadu, India, provided research facilities and assistance.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTEREST

The Authors declare no conflicts of interest.

REFERENCES

1. Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. Journal of diabetes research. 2013 Oct;2013.

2. Strachan MW, Reynolds RM, Frier BM, Mitchell RJ, Price JF. The role of metabolic derangements and glucocorticoid excess in the aetiology of cognitive impairment in type 2 diabetes. Implications for future therapeutic strategies. Diabetes, Obesity and Metabolism. 2009 May;11(5):407-14.

3. Asfaha S, Padwal R. Antihypertensive drugs and incidence of type 2 diabetes: evidence and implications for clinical practice. Current hypertension reports. 2005 Sep;7(5):314-22.

4. Elnaem MH, Mohamed MH, Huri HZ, Azarisman SM, Elkalmi RM. Statin therapy prescribing for patients with type 2 diabetes mellitus: a review of current evidence and challenges. Journal of pharmacy & bioallied sciences. 2017 Apr;9(2):80.

5. Canguven O, Talib RA, El Ansari W, Yassin DJ, Al Naimi A. Vitamin D treatment improves levels of sexual hormones, metabolic parameters and erectile function in middle-aged vitamin D deficient men. The Aging Male. 2017 Jan 2;20(1):9-16.

6. Basat S, Sivritepe R, Ortaboz D, Sevim Çalık E, Küçük EV, Şimşek B, Atay S, Çalışgan A. The relationship between vitamin D level and erectile dysfunction in patients with type 2 diabetes mellitus. The Aging Male. 2018 Apr 3;21(2):111-5.

7. Papadopoulos V, Li L, Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone?. Andrology. 2021 Jan;9(1):65-72.

8. Deng C, Zhang Z, Li H, Bai P, Cao X, Dobs AS. Analysis of cardiovascular risk factors associated with serum testosterone levels according to the US 2011–2012 National Health and Nutrition Examination Survey. The Aging Male. 2018 Jun 20.

9. Rabijewski M, Papierska L, Kuczerowski R, Piątkiewicz P. Hormonal determinants of erectile dysfunction and lower urinary tract symptoms in middle-aged and elderly men with prediabetes. The Aging Male. 2015 Oct 2;18(4):256-64.

10. Rabijewski M, Papierska L, Kuczerowski R, Piątkiewicz P. Hormonal determinants of erectile dysfunction and lower urinary tract symptoms in middle-aged and elderly men with prediabetes. The Aging Male. 2015 Oct 2;18(4):256-64.

11. Morgunov LY, Denisova IA, Rozhkova TI, Stakhovskaya LV, Skvortsova VI. Hypogonadism and its treatment following ischaemic stroke in men with type 2 diabetes mellitus. The Aging Male. 2020 Jan 2;23(1):71-80.

12. Haider KS, Haider A, Doros G, Traish A. Long-term testosterone therapy improves urinary and sexual function, and quality of life in men with hypogonadism: results from a propensity matched subgroup of a controlled registry study. The Journal of Urology. 2018 Jan;199(1):257-65.

13. Groti K, Žuran I, Antonič B, Foršnarič L, Pfeifer M. The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. The Aging Male. 2018 Jul 3;21(3):158-69.

14. Saad F, Yassin A, Almehmadi Y, Doros G, Gooren L. Effects of long-term testosterone replacement therapy, with a temporary intermission, on glycemic control of nine hypogonadal men with type 1 diabetes mellitus–a series of case reports. The Aging Male. 2015 Jul 3;18(3):164-8.

15. Yassin A, Nettleship JE, Talib RA, Almehmadi Y, Doros G. Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. The Aging Male. 2016 Jan 2;19(1):64-9.

16. Hatami H, Parizadeh D, Bidhendi Yarandi R, Tohidi M, Ramezani Tehrani F. Endogenous testosterone does not improve prediction of incident cardiovascular disease in a community-based cohort of adult men: results from the Tehran Lipid and Glucose Study. The Aging Male. 2020 Oct 1;23(4):243-50.

17. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes care. 2007 Apr 1;30(4):911-7.

18. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, Dobs A, Basaria S, Golden SH, Platz EA. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes care. 2007 Feb 1;30(2):234-8.

19. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT. Sex hormones, inflammation and the metabolic syndrome: a population-based study. European journal of endocrinology. 2003 Dec 1;149(6):601-8.

20. Phillips GB, Jing T, Heymsfield SB. Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. Metabolism. 2003 Jun 1;52(6):784-90.

21. Haffner SM, Karhapää P, Mykkänen L, Laakso M. Insulin resistance, body fat distribution, and sex hormones in men. Diabetes. 1994 Feb 1;43(2):212-9.

22. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. European Journal of Endocrinology. 2006 Jun 1;154(6):899-906.

23. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. The Aging Male. 2003 Jan 1;6(1):1-7.

24. Mårin P, Holmäng S, Jönsson L, Sjöström L, Kvist H, Holm G, Lindstedt G, Björntorp P. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity. 1992 Dec 1;16(12):991-7.

25. Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, Gouault-Heilmann M, Lemort N, Thibult N, Joubert E, Balkau B, Eschwege E. Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. Diabetes care. 2001 Dec 1;24(12):2149-51.

26. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2010 Jun 1;95(6):2536-59.

27. Boots LR, Potter S, Potter HD, Azziz R. Measurement of total serum testosterone levels using commercially available kits: high degree of between-kit variability. Fertility and sterility. 1998 Feb 1;69(2):286-92.

28. Bhasin S, Pencina M, Jasuja GK, Travison TG, Coviello A, Orwoll E, Wang PY, Nielson C, Wu F, Tajar A, Labrie F. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. The Journal of Clinical Endocrinology & Metabolism. 2011 Aug 1;96(8):2430-9.

29. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. The Journal of Clinical Endocrinology & Metabolism. 2007 Feb 1;92(2):405-13.

30. Putta S, Peluso I, Yarla NS, Kilari EK, Bishayee A, Lu DY, Barreto GE, Ashraf GM, Scotti L, Scotti MT, Singla RK. Diabetes mellitus and male aging: Pharmacotherapeutics and clinical implications. Current pharmaceutical design. 2017 Aug 1;23(30):4475-83.

31. Vermeulen A. Physiology of the testosterone-binding globulin in man. Annals of the New York Academy of Sciences. 1988 Sep;538(1):103-11.

32. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone–binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes care. 2004 May 1;27(5):1036-41.

33. Fukui M, Kitagawa Y, Nakamura N, Kadono M, Mogami S, Hirata C, Ichio N, Wada K, Hasegawa G, Yoshikawa T. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. Diabetes care. 2003 Jun 1;26(6):1869-73.

34. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. Jama. 2006 Mar 15;295(11):1288-99.

35. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, Dobs A, Basaria S, Golden SH, Platz EA. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes care. 2007 Feb 1;30(2):234-8.

36. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, MacIsaac RJ, Clarke S, Zajac JD, Jerums G. Low testosterone levels are common and associated with insulin resistance in men with diabetes. The journal of clinical endocrinology & metabolism. 2008 May 1;93(5):1834-40.

37. Sikaris K, McLachlan RI, Kazlauskas R, De Kretser D, Holden CA, Handelsman DJ. Reproductive hormone reference intervals for healthy fertile young men: evaluation of automated platform assays. The Journal of Clinical Endocrinology & Metabolism. 2005 Nov 1;90(11):5928-36.

38. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes care. 2007 Apr 1;30(4):911-7.

39. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2004 Nov 1;89(11):5462-8.

40. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT. Sex hormones, inflammation and the metabolic syndrome: a population-based study. European journal of endocrinology. 2003 Dec 1;149(6):601-8.

41. Muller M, Grobbee DE, Den Tonkelaar I, Lamberts SW, Van Der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. The Journal of Clinical Endocrinology & Metabolism. 2005 May 1;90(5):2618-23.

42. Stellato RK, Feldman HA, Hamdy OS, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. Diabetes care. 2000 Apr 1;23(4):490-4.

43. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. Diabetes care. 2002 Jan 1;25(1):55-60.

44. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone–binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes care. 2004 May 1;27(5):1036-41.

45. Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. The Journal of Clinical Endocrinology & Metabolism. 2006 Mar 1;91(3):843-50.

46. Haring R, Völzke H, Felix SB, Schipf S, Dörr M, Rosskopf D, Nauck M, Schöfl C, Wallaschofski H. Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania. Diabetes. 2009 Sep 1;58(9):2027-31.

47. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, Morales AM, Volterrani M, Yellowlees A, Howell JD, Channer KS. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes care. 2011 Apr 1;34(4):828-37.

48. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K. Adverse events associated with testosterone administration. New England Journal of Medicine. 2010 Jul 8;363(2):109-22.

49. Kuehn BM. Testosterone trial halted. JAMA. 2010 Aug 25;304(8):846-.

50. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. The Journal of Clinical Endocrinology & Metabolism. 2012 Jun 1;97(6):2050-8.

51. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013 Dec 1;169(6):725-33.

52. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. Jama. 2013 Nov 6;310(17):1829-36.

53. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni Jr JF, Hoover RN. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PloS one. 2014 Jan 29;9(1):e85805.

54. Cai X, Tian Y, Wu T, Cao CX, Li H, Wang KJ. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Asian journal of andrology. 2014 Jan;16(1):146.

55. Baillargeon J, Urban RJ, Kuo YF, Ottenbacher KJ, Raji MA, Du F, Lin YL, Goodwin JS. Risk of myocardial infarction in older men receiving testosterone therapy. Annals of Pharmacotherapy. 2014 Sep;48(9):1138-44.