Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Rezanezhad B, Borgquist R, et al., 2023. Testosterone Level and Risk of Diabetes: Follow-Up Study, Medical Research Archives, [online] 11(9). https://doi.org/10.18103/mra.v11i9.4473

DOI
https://doi.org/10.18103/mra.v11i9.4473

ISSN: 2375-1924

RESEARCH ARTICLE

Testosterone Level and Risk of Diabetes: Follow-Up Study

***Babak Rezanezhad, MD**
Department of Clinical Sciences, Cardiology, Lund University Hospital, Lund, Sweden.

Rasmus Borgquist, MD, PhD, Associate Professor
Department of Clinical Sciences, Cardiology, Lund University Hospital, Lund, Sweden.

Saad Elzanaty, MD, PhD, Associate Professor
Department of Translational Medicine, Skåne University Hospital, Lund University, Malmö, Sweden.

***Correspondence to:** babak.rezanezhad_zanjani@med.lu.se

ABSTRACT:
Background: Epidemiological studies have documented an inverse relationship between testosterone levels and risk of cardiovascular disease. The present study aimed to explore the association between testosterone levels and risk of developing diabetes mellitus from 108 middle-aged men with no history of medical diseases.
Methods: Data regarding the age of subjects, smoking, alcohol consumption, waist-to-hip ratio, and family history of cardiovascular disease were collected at the time of inclusion. Testosterone levels were also measured. 15 years later the medical history of the men was reviewed to record the development of medical incidents with references to diabetes mellitus. Two groups of men were identified based on testosterone levels: hypogonadal (testosterone ≤12 nmol/L) and eugonadal (testosterone >12 nmol/L).
Results: In total, 10 (9.0%) out of 108 men developed diabetes during the 15-year follow-up period, of whom 6 (16%) out of 37 and 4 (6%) out of 71 were men in the hypogonadal and eugonadal cohorts respectively (p=0.08). Using Cox proportional hazards regression analysis, the adjusted risk for diabetes was significantly lower in eugonadal men compared to hypogonadal men (adjusted hazard ratio=0.236; 95% CI=0.062–0.898; P=0.03).
Conclusion: Our results showed a significant increased risk of diabetes in men with low testosterone levels compared to men with normal testosterone.
Keywords: Diabetes, Hypertension, Hypogonadism, Eugonadism, Testosterone.

Introduction:

Low testosterone in men is a result of several disorders including primary testicular dysfunction, hypothalamic-pituitary diseases, androgen deprivation therapy, and the aging process. Men with low testosterone have decreased muscle bulk, increased adverse cardiovascular events, and insulin resistance & diabetes mellitus (DM) compared to men with normal testosterone. [1,2]

The prevalence of DM has increased rapidly in recent years, [3] with type 2 DM accounting for about 90% of individuals with DM. [4,5] Known demographic factors for DM including family history of DM, [6] socioeconomic disadvantages, [7] and male sex & old age. [3,7,8] DM is a leading cause of cardiovascular disease. [9]

In a cross-sectional study based on 355 male patients with type 2 DM aged 32-83 years, 17 % hade severe hypogonadism (testosterone less than 8 nmol/L), and 25 % with mild hypogonadism (testosterone 8–12 nmol/L). [1] In a similar study based on 203 male patients with type 2 DM aged 30-86 years, 17 % hade severe hypogonadism (testosterone less than 8 nmol/L), and 18 % with mild hypogonadism (testosterone 8–12 nmol/L), [11] indicating an association between DM and testosterone. However, the nature of those two studies did not solve the issue of whether low testosterone observed in diabetic men is consequence or a contributing factor. In a population-based prospective cohort study, 54 (5%) out of 1030 men aged 40-70 years develop diabetes after a mean follow-up period of 9 years. The risk of developing diabetes was 1.58 for a decrease of 1 SD in free testosterone (0,14 nmol/L). However, the number of men with low testosterone levels at baseline who develop DM was not given. [12] In a similar study, 57 (8 %) of 702 men aged 42-60 years develop DM during a follow-up period of 11 years. However, the association between total testosterone and risk for DM disappeared when adjusted for age, smoking, alcohol consumption, history of cardiovascular disease (CVD), waist-to-hip ratio, systolic blood pressure, concentrations of insulin; glucose; and triglycerides. [13] In another longitudinal study, 76 (5 %) out of 1454 men aged 25-84 years developed DM during a followed-up period of 9 years, thirty-three out of the seventy-six were men with low baseline testosterone less than 9.9 nmol/L. However, the number of men with low testosterone levels who did not develop DM was not given. [14] Interestingly, testosterone treatment with intramuscular undecanoate for at least 8 years prohibited the progression of prediabetes to type 2 diabetes as well as improvement of glucose metabolism in men with testosterone level ≤ 12.1 nmol/L. [15]

In an attempt to understand whether low testosterone observed in men with type 2 DM is a consequence or a contributing factor for DM, the present study explored the association between testosterone and risk for diabetes in a group of middle-aged men with no history of medical diseases and not receiving any medications, taken into consideration different co-variables that could affect such an association.

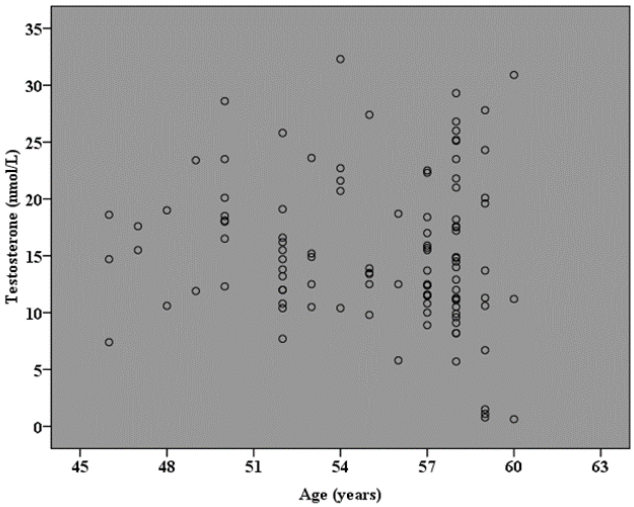

Figure I: Distribution of testosterone according to the age of subjects.

Methods:

STUDY POPULATION:

This longitudinal, observational study is based on information from 108 middle-aged (45-60 years) men from the general population with no history of medical disease and who were not receiving any medications 6 months before the date of inclusion in a study about the association between erectile dysfunction and risk of cardiovascular disease. Detailed information about the recruitment and characteristics of the participants has been previously published. [16]

FOLLOW-UP

The data was collected between 2006 and 2011. The number of men was as follows: 2006/ 42 (39%), 2007/20 (18%), 2008/12 (11%), 2009/17 (16%), 2010/15 (14%), 2011/2 (2%). In 2021 the medical information on the men was reviewed to record the development of DM.

OUTCOME AND VARIABLES:

The outcome of interest was a new DM diagnosis after the inclusion date. DM diagnosis was defined as the receipt of outpatient care, including the

prescription of related medicines. Several potential co-factors for DM including the age of subjects, waist-to-hip ratio, smoking, alcohol consumption, and family history of CVD were considered in statistical analyses. Waist-to-hip ratio was found to be superior to BMI in predicting metabolic syndrome and DM type 2. [17,18]

LABORATORY MEASUREMENTS:
The subjects included in the study were asked to deliver a blood sample (5 mL) for analysis of testosterone. Samples were collected between 07:00 and 10:00 PM and were centrifuged at 1000 g for 10 minutes. After centrifugation, serum was kept at -80 °C until assay. Serum testosterone concentrations were measured using the Two-step competitive method with Electro Chemi Luminiscence Immunoassay (ECLI) detection technique based on Ruthenium (Ru) derivatives, with an intra-and interassay coefficient of variation (CV) of 5%, and a reference range 5.0–30 nmol/L (Department of Clinical Chemistry, Malmö University Hospital, Malmö, Sweden). Different cut-off points for normal testosterone were used including values > 8 nmol/L, [19] and > 10 nmol/L. [20] In the present study, we decided to refer to values > 12 nmol/L. [1]

The Institutional Review Board Committee at Lund University of Medical sciences reviewed and approved the design of the study. Written informed consent was obtained from each participant. DNR 400/2005.

Statistical analyses:

Statistical analyses were made using the SPSS software, version 16 (SPSS, Inc; Chicago, IL). Nine men had testosterone levels ≤ 8.0 nmol/L, and 17 men had testosterone levels ≤ 10 nmol/L, being few to run adequate statistical analyses. Therefore, we decided to divide men into two groups: testosterone ≤ 12 nmol/L (hypogonadal) and testosterone > 12 nmol/L (eugonadal) in order to increase the statistical power of the study.

Both non-parametric Mann–Whitney U test, and Fisher's exact test were used to evaluate differences between men who were classified as being hypogonadal (testosterone ≤ 12 nmol/L), and those who were classified as being eugonadal (testosterone > 12 nmol/L) including age of subjects (years), waist-to-hip ratio, smoking (never, past/current), alcohol consumption (yes, no), and family history of CVD (yes, no).

Cox proportional hazards regression analysis was used to examine the crude and adjusted hazard ratios (HR) for DM in the hypogonadal men (reference) compared with the eugonadal men during the follow-up period after adjustment for the age of subjects (continuous years), smoking (never, past/current), alcohol consumption (yes, no), waist-to-hip ratio, and family history of CVD (yes, no). A two-sided P value less than 0.05 was considered statistically significant.

Results:

The hypogonadal and eugonadal group included 37 and 71 men respectively. Figure 1 showing the distribution of testosterone according the age of subjects. The distributions of sociodemographic characteristics of the hypogonadal and eugonadal men are presented in Table 1. The hypogonadal men were relatively older than the eugonadal men (56 years vs. 55 years, p = 0.03). Waist-to-hip ratio, smoking, alcohol consumption, and family history of CVD did not differ significantly between groups (p > 0.05) (Table I).

In total, 10 (9.0 %) out of 108 men developed diabetes during the follow-up period, of whom 6 (16 %) of 37 and 4 (6.0 %) of 71 were men in the hypogonadal and eugonadal men respectively (Table II). Using Cox proportional hazards regression analysis, the crude HR for DM was 0.32 (95 % CI = 0.091–1.149, p = 0.08). After adjustment for the potential co-factors: age of subjects, waist-to-hip ratio, smoking, alcohol consumption, and family history of CVD the adjusted HR for developing DM was 0.24 (95% CI = 0.062–0.898; P = 0.03) (Table II).

Discussion:

The present study examined the association between baseline testosterone levels and the risk of developing DM in 108 middle-aged men from the general population with no history of medical disease. Men with low testosterone levels at baseline were associated with increased risk of DM compared to men with normal testosterone at baseline. Thus, in the adjusted Cox regression analysis model, the present study found a negative significant association between baseline testosterone levels and risk of developing DM. The probability of developing DM decreased by 76 % in men with normal testosterone at baseline. Our results are in line with previous reports, [12-14] indicating that men with low testosterone levels are at increased risk for DM.

Table 1: Demographic characteristics of the study subjects, stratified by low (≤ 12 nmol/L) and normal (> 12 nmol/L) testosterone levels obtained from 108 middle-aged Swedish men from the general population.

Variables	Hypogonadal men (Testosterone ≤ 12 nmol/L) n = 37	Eugonadal men (Testosterone > 12 nmol/L) n = 71	P-value
Age (Years)	56 (±4.0)	55 (±4.0)	0.03
Waist-to-hip ratio	1.02 (±0.06)	1.16 (±0.06)	0.09
Smoking[f]			
Never	4.0 (11)	19 (27)	0.08
Past/current	33 (89)	52 (73)	
Alcohol consumption[f]			
Yes	30 (81)	59 (83)	1.00
No	6.0 (16)	11(15)	
Family history of CVD[f]			
Yes	12 (32)	19 (27)	0.80
No	27 (73)	51(72)	

Data are mean (±SD) or number (%). Statistical analyses were performed using the Mann Whitney U test. Fisher exact test[f]. CVD = cardiovascular diseases. P values less than 0.05 were considered statistically significant.

Table II: Hazard ratios (HR) for diabetes in men with and without normal testosterone obtained from 108 middle-aged Swedish men from the general population who were followed up for 15 years.

Variables	Total n = 108		Hypogonadal men (Testosterone ≤ 12 nmol/L) n = 37		Eugonadal men (Testosterone > 12 nmol/L) n = 71		P-value
	n	%	n	%	n	%	
Development of diabetes							
Yes	10	9.0	6.0	16	4.0	6.0	
Crude HR			Reference		0.324 (0.091–1.149)		0.08
Adjusted HR			Reference		0.236 (0.062–0.898)		0.03

Both crude and adjusted HR were calculated using Cox proportional hazard regressions. Adjustments were made for age of subjects (continuous years), waist-to-hip ratio, smoking (never, current/past), alcohol consumption (yes, no), and family history of CVD (yes, no). A P value less than 0.05 was considered statistically significant.

Explanations of increased risk of DM in men with low testosterone including changes in body composition: increased visceral fat and decreased skeletal muscle mass often seen in men with low testosterone, [7] all of which are known risk factors for DM. [6,21] It is estimated that 90 % of diabetic patients are overweight. [22] Insulin resistance and insulin deficiency are two major pathophysiological events that connecting obesity and diabetes. [23] Additionally, excessive visceral fat is a reason for chronic inflammation, which is known to contribute to common diseases such as DM. [24] An inverse relationship was found between testosterone and inflammatory markers. [16,26] Studies from testosterone replacement therapy in hypogonadal men treated with testosterone replacement therapy reported an improvement of inflammatory markers and glucose levels. [27,28]

Hyperlipidemia, characterized by reduced circulating high-density lipoprotein cholesterol, elevated circulating low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol, is not only risk factor for cardiovascular diseases but also for DM.[29,30] Hyperlipidemia is also attributed to insulin resistance and insulin deficiency. An inverse relationship between testosterone levels and lipid profile was previously found.[16,31] Testosterone replacement therapy improves the lipid profile and reduces insulin resistance and improves glycemic control in hypogonadal men with Type 2 diabetes.[32]

Type 2 diabetes mellitus was almost 2.5 times as likely to develop in subjects with hypertension as in subjects with normal blood pressure. Higher blood pressure was shown to induce microvascular dysfunction, which may contribute to the pathophysiology of diabetes development.[33,34] Endothelial dysfunction, which is related to insulin resistance, is also strongly associated with hypertension, and biomarkers of endothelial dysfunction were found to be independent predictors of Type 2 diabetes.[35] Testosterone is negatively associated with systolic blood pressure.[36]

Additionally, Maneschi et al investigated the effects of testosterone treatment on insulin signalling by analysing the intracellular localization of glucose uptake and glucose transporter 4 (GLUT4) in animal study, and found that GLUT4 membrane translocation was significantly reduced in 32 rabbits treated with a high fat diet compared to 35 rabbits exposed to a regular diet, while it was preserved in visceral adipose tissue from 19 rabbits exposed to a high fat diet and treated with intramuscular injection of testosterone (30 mg/kg, weekly for 12 weeks),[37] indicating a link between lower testosterone and insulin resistance. Moreover, treatment with testosterone undecanoate prevented the progression of prediabetes to type 2 diabetes and improve glucose metabolism in men at high risk of, or with newly to type 2 diabetes.[15, 38]

The results from studies on the effect of insulin sensitizing agent (thiazolidinedione, rosiglitazone 8 mg/d) on serum testosterone levels were controversial. Vierhapper et al observed a reduction of testosterone levels in ten healthy, non-obese men aged 21 to 35 years. [39] On the other hand, Kapoor et al showed an improvement of testosterone levels in 15 hypogonadal diabetic men aged 37 to 75 years. [40] The difference between the two studies could be attributed to the very short period of follow up in the first study, being based on weeks compared to 6 months in the later study.

In contrast, higher testosterone levels associated with an increased risk for Type 2 diabetes in woman related to adiposity, reduced insulin-mediated glucose uptake, and increases lipogenesis. [41, 42]

The strength of the study is the extended period of follow up; data about the blood glucose levels and glucose tolerance test was accessed in all the ten men who develop DM later, and all had normal values. On the other hand, the present study is based on a small number of participants, and testosterone concentrations were measured once for each participant. Moreover, the assessment of DM was based on data collected from each man's medical records (receiving medical care or prescription of medicines owing to DM), since there is no screening system for DM; men who probably had DM but did not develop clinical symptoms owing to DM were not included, so the results of the present study should be interpreted with caution.

Conclusions:

Men having normal testosterone levels are associated with an almost 75 % lower risk of developing diabetes.

Author contributions:

Dr. Rezanezhad participated in research design, writing the paper, the performance of the research, and data analysis.
Dr. Borgquist participated in research design and writing the paper.
Dr. Elzanaty participated in research design, writing the paper, the performance of the research, and data analysis.

Conflicts of Interest:

The authors declare no conflict of interest.

References:

1. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS. Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010; 95(6):2536-2559.
2. Yeap BB. Androgens and cardiovascular disease. Curr Opin Endocrinol Diabetes Obes. 2010; 17(3):269-276.
3. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and prediabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care. 2009; 32(2):28794.
4. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: Principles of pathogenesis and therapy. Lancet. 2005; 365(9467):1333-1346
5. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001; 414(6865):482-487.
6. Magliano DJ, Barr EL, Zimmet PZ, Cameron AJ, Dunstan DW, Colagiuri S, et al. Glucose indices, health behaviors, and incidence of diabetes in Australia: The Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care. 2008; 31(2):267-72.
7. Atlantis E, Lange K, Wittert GA. Chronic disease trends due to excess body weight in Australia. Obes Rev. 2009;10(5):543-53
8. Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, et al. The rising prevalence of diabetes and impaired glucose tolerance: The Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care. 2002; 25(5):829-34.
9. Barr EL, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 2007; 116(2):151-7.
10. 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; 30(4):911-7
11. Ogbera OA, Chinenye S, Olufemi F, Wale A. Hypogonadism, and subnormal total testosterone levels in men with type 2 diabetes mellitus. J Coll Physicians Surg Pak. 2011;21(9):517-521
12. Stellato RK, Feldman HA, Hamdy O, 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; 23(4):490-494.
13. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care. 2004; 27(5):1036-1041.
14. Vikan T, Schirmer H, Njølstad I, Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. Eur J Endocrinol. 2010; 162(4):747-54.
15. Yassin A, Haider A, Haider KS, Caliber M, Doros G, Saad F, et al. Testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes: eight-year data from a registry study. Diabetes Care. 2019; 42(6):1104-11.
16. Rezanezhad B, Borgquist R, Willenheimer R, Elzanaty S. The Association between Serum Testosterone and Risk Factors for Atherosclerosis. Curr Urol. 2019; 13(2):101-106.
17. Bener A, Yousafzai MT, Darwish S, Al-Hamaq AOAA, Nasralla E A, et al. Obesity Index That Better Predict Metabolic Syndrome: Body Mass Index, Waist Circumference, Waist Hip Ratio, or Waist Height Ratio. J Obes. 2013;2013:1-9.
18. Hardy DS, Stallings DT, Garvin JT, Gachupin FC, Xu H, Racette SB. Anthropometric discriminators of type 2 diabetes among White and Black American adults. J Diabetes. 2017;9(3):296-307.
19. Arver S & Lehtihet M. Current guidelines for the diagnosis of testosterone deficiency. Frontiers of Hormone Research. 2009;37:5-20.
20. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2006;91(6):1995-2010.
21. Tirosh A, Shai I, Bitzur R, Kochba I, Tekes-Manova D, Israeli E, et al. Changes in triglyceride levels over time and risk of type 2 diabetes in young men. Diabetes Care. 2008;31(10): 2032-7.
22. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world-a growing challenge. N Engl J Med. 2007; 356(3):213-5.

23. Felber JP & Golay A. Pathways from obesity to diabetes. Int J Obes Relat Metab Disord. 2002;26 suppl 2:39-45.
24. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793-1801.
25. Bobjer J, Katrinaki M, Tsatsanis C, Giwercman YL, Giwercman A. Negative association between testosterone concentration and inflammatory markers in young men: a nested cross-sectional study. PLoS One. 2013,18;8(4):e61466
26. Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, et al. The relationship between testosterone and molecular markers of inflammation in older men. J Endocrinol Invest. 2005;28(11 Suppl Proceedings):116-9.
27. Maggio M, Blackford A, Taub D, Carducci M, Ble A, Metter EJ, et al. Circulating inflammatory cytokine expression in men with prostate cancer undergoing androgen deprivation therapy. J Androl. 2006;27(6):725-728.
28. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab. 2004; 89(7):3313-3318
29. Su X & Peng D. New insight into sortilin in controlling lipid metabolism and the risk of atherogenesis. Biol Rev. 209;95(1):232-43.
30. Ruscica M, Ferri N, Macchi C, Corsini A, Sirtori CR. Lipid lowering drugs and inflammatory changes: an impact on cardiovascular outcomes? Ann Med. 2018;50(5):461-84.
31. Kupelian V, Chiu GR, Araujo AB, Williams R E, Clark R V, McKinlay JB. Association of sex hormones and C-reactive protein levels in men. Clin Endocrinol (Oxf). 2010;72(4):527-533.
32. Magnussen LV, Glintborg D, Hermann P, Hougaard DM, Højlund K, Andersen M. Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2 diabetes on metformin monotherapy. Diabetes Obes Metab. 2016;18(10):980-9.
33. Feihl F, Liaudet L, Waeber B, Levy BI. Hypertension: a disease of the microcirculation? Hypertension. 2006;48(6):1012-1017
34. Nguyen TT, Wang JJ, Islam FM, Mitchell P, Tapp RJ, Zimmet PZ, et al. Retinal arteriolar narrowing predicts incidence of diabetes: The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. Diabetes. 2008;57(3):536-9.
35. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2004;291(16):1978-1986.
36. Rezanezhad B, Borgquist R, Elzanaty S. Association between Testosterone Levels and Clinical Markers of Atherosclerosis. Annals of Clinical and Medical Case Reports. 2020;4(6):1-5
37. Maneschi E, Morelli A, Filippi S, Cellai I, Comeglio P, Mazzanti B, et al. Testosterone treatment improves metabolic syndrome-induced adipose tissue derangements. J Endocrinol. 2012;215(3):347-62.
38. Wittert G, Bracken K, Robledo KP, Grossmann M, Yeap BB, Handelsman DJ, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol. 2021;9(1):32-45.
39. Vierhapper H, Nowotny P, Waldha W. Reduced Production Rates of Testosterone and Dihydrotestosterone in Healthy Men Treated With Rosiglitazone. Metabolism. 2003;52(2):230-2
40. Kapoor D, Channer KS, Jones TH. Rosiglitazone increases bioactive testosterone and reduces waist circumference in hypogonadal men with type 2 diabetes. Diabetes Vasc Dis Res.2008;5(2):135-7.
41. Oh JY, Barrett-Connor E, Wedick NM, Wingard D L. Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo study. Diabetes Care. 2002;25(1):55-60
42. Ding E L, Song Y, Manson J E, Buring JE, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia. 2007;50(10):2076-2084.