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The effect of serum free testosterone level on glycemic control and atherosclerosis in type 2 diabetic men

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Abstract: Background: Atherosclerosis is a complex disease of the arteries characterized by endothelial dysfunction, vascular inflammation, and the build-up of lipids within the intima of the vessel wall. Testosterone has a central or permissive role in pathogenesis of the metabolic syndrome and type 2 diabetes. Insulin resistance is associated with several CVD risk factors such as obesity, dyslipidaemia, hypertension and the proinflammatory state. We aim to disclose the relationship between serum testosterone concentration and carotid atherosclerosis and its risk factors in men with type 2 diabetes. Patients and methods: The study population comprised 123 consecutive men of Type 2 diabetes. Retinopathy and nephropathy were ranked and graded respectively. Cardiovascular disease was defined as the presence of previous myocardial infarction or cerebral infarction. Total cholesterol and triglyceride concentrations were determined and hemoglobin Alc was measured. Assessment for the presence of carotid atherosclerosis was done, using ultrasonographic measurement of carotid intima media thickness (IMT). The relationship between serum testosterone concentration and carotid intima-media thickness IMT was investigated in all patients. Results: The mean of IMT for all patients was 0.96 ± 0.28 mm. Mean IMT was significantly greater in patients with lower concentrations of F-tes than in patients with higher concentrations of F-tes. (P= 0.038). Relationship between serum free testosterone concentration and other variables showed a negative correlation with patients' age, patients' age at onset, duration of diabetes, BMI, HbA_{1c}, systolic and diastolic blood pressure, and total cholesterol concentrations and mean IMT in men with type 2 diabetes. No significant correlation was found between F-tes with triglyceride and negative correlation with mean IMT. Conclusion: Serum free testosterone concentration was found to be low in type 2 diabetic men. It has a negative correlation with patients' age, patients' age at onset of the disease, duration of diabetes, BMI and HbA1c, total cholesterol concentrations systolic and diastolic blood pressure and mean IMT. This may disclose the different mechanisms played by testosterone in the pathogenesis of cardiovascular risk in men with type 2 diabetes.

Keywords: Testosterone, Atherosclerosis, Type 2 Diabetes Mellitus

1. Introduction

Atherosclerosis is a complex disease of the arteries characterized by endothelial dysfunction, vascular inflammation, and the build-up of lipids within the intima of the vessel wall (1). Men develop coronary artery disease and experience coronary events about 10 years earlier than women. Historically, this was always thought to be related to the protective effects of female sex hormones. Testosterone is an important anabolic hormone and has an anti-insulin effect (2). Testosterone has a central or permissive role in pathogenesis of the metabolic syndrome and type 2 diabetes (3). One of the most important underlying causes of insulin resistance is associated with low testosterone levels to men (4). Studies have reported that men with type 2 diabetes mellitus (T2DM) have a high prevalence of low serum testosterone (5-7). Further, reduced total testosterone (TT) levels have been associated with insulin resistance and subsequent risk for developing T2DM (8, 9).

Insulin resistance is associated with several cardiovascular disease (CVD) risk factors such as obesity, dyslipidaemia, hypertension and the proinflammatory state. Moreover, insulin resistance is one of the major pathophysiological mechanisms leading to abnormalities in glucose tolerance, which further enhances the risk of CVD (10). Insulin elicits metabolism-independent cardioprotection against myocardial ischaemic injury and the development of atherosclerosis, hypertension and heart failure, in which bio-available nitric oxide (NO) plays a significant role as a second messenger of insulin mediated survival signals. Furthermore, interruption of insulin signaling with the endogenous cardiovascular NO system is participatory in the pathogenesis of insulin resistance and its cardiovascular complications (11).

Since the direct association between the testosterone deficiency and cardiovascular risk remains controversial, we aim to disclose the relationship between serum free testosterone concentration and carotid atherosclerosis and its risk factors in men with type 2 diabetes.

2. Patients and Methods

The protocol for the research project was approved by a suitably constituted ethics committee of the hospital, and it is conformed to the provision of the World Medical Association's Declaration of Helsinki. An informed consent has been obtained for all investigations on subjects of the study (and patient anonymity was preserved).

2.1. Study Populations

The study population comprised 123 consecutive men of type 2 diabetes as diagnosed according to the Report of the Expert Committee on tire Diagnosis and Classification of Diabetes Mellitus (12). The study was applied From January 2012to June 2013.

2.2. Clinical Assessment

Retinopathy was ranked as follows: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), and proliferative diabetic retinopathy (PDR). Nephropathy was graded as follows: normal albuminuria, urinary albumin excretion (UAE) <30 mg/g creatinine (Cr); microabuminuria, UAE 30-300 mg/g Cr; or macroalbuminuria, UAE >300 mg/g Cr.

CVD was defined as the presence of previous myocardial infarction or cerebral infarction based on the clinical history or physical examination.

Exclusion Criteria

1. Patients with major organ failure (heart, respiratory, liver, or renal failure).
2. Patients with cancer prostate, prostatectomy, castration or that receiving androgen deprivation therapy.
3. Patients receiving androgens, steroids, or hypolipidemic medications.
4. Patients with hepatitis C virus infection. [because this infection has been reported to cause atherosclerosis (13)].
5. Smoker patients and controls [to avoid the possible interaction between smoking and testosterone serum level (14)].
6. Those with active infection or autoimmune diseases.

2.3. Laboratory Investigations

- Total cholesterol and triglyceride concentrations were determined by standard techniques.
- Hemoglobin HbA_{1c} was measured immunoturbidimetrically (Using COBAS INTEGTRA 400 machine; Roche Diagnostics, Indianapolis.Ind).
- Serum free testosterone F-tes concentrations were measured in 123 consecutive men with type 2 diabetes using Microparticle Enzyme Immunoassay (MEA) on AX SYM system F-tes kit (normal ranges 14.0- 40.0 pg/ml).

2.4. Assessment for the Presence of Carotid Atherosclerosis using Ultrasonographic Measurement of Carotid Intima -Media Thickness (IMT)

B-mode ultrasonographic imaging of the carotid artery was performed using hp SO-NOS 5500 machine with high-resolution, real-time ultrasonography with a 10-MHz transducer. The examination and image analysis were performed by a trained sonographer who remained unaware of other data and whose duplex results have been previously validated. High-resolution B-mode carotid ultrasonography was performed with HDI 5000 ATL machine (Phillipis Medical Systems). The subject lay supine with the neck extended and the chine turned contralateral to the side being examined. Scanning involved examination of carotid arteries in transverse and longitudinal planes. The right and left carotid arteries were scanned for measurement of IMT in both the longitudinal and transverse projections over an arterial segment including 30 mm of the distal common carotid artery, the bifurcation, and 15 mm of the internal carotid artery (15). IMT was measured in the far wall of the vessel as the distance from the leading edge of the lumen- intima interface to the leading edge of the intima - adventitia interface. The average measurement was taken as the mean IMT.

The relationship between serum testosterone concentration and carotid intima-media thickness IMT was investigated in all patients. Also, the relationships between serum testosterone concentrations and major cardiovascular risk factors were evaluated, including age, blood pressure, serum lipid profile, and glycemic control (HbA_{1c}), BMI, severity of diabetic retinopathy, severity of diabetic nephropathy, or presence of CVD.

2.5. Statistical Analysis

Data were collected, revised and then analyzed using SPSS version 10.

Quantitative variables were expressed as mean and standard deviation using unpaired- *t* tests for equality of means. Spearman correlation coefficient was used to correlate between serum testosterone and other variables.

A significant statistical was considered with *p* value <0.05.

3. Results

3.1. Study Population

Demographic, clinical and laboratory data of the patients are summarized in Table 1. The study group comprised 123 men type 2 diabetic patients with a mean age of 60.0 ±7.9 years. Mean age at onset was 49.0±9.7 years with mean disease duration was 11.2 ± 7.1 years. Mean of BMI was 29.11 ± 3.41, HbA_{1c} (%) was 7.5 ±1.6, mean systolic and diastolic blood pressure were 146.70 ±9.02 and 91.76 ±9.36 respectively. Laboratory data of the patients' revealed mean total cholesterol of 194.84 ±33.20 mg/dl (with levels of triglyceride, HDL cholesterol are 151.42 ±15.84 mg/dl and 38.38 ± 3.07 mg/dl respectively). Numbers of patients with different ranks of Retinopathy and Nephropathy are enumerated. F-tes was found to be 10.6±3.8 pg/ml.

3.2. Carotid Duplex Study and Measurement of IMT Results

The mean of IMT for all patients [right + left/2] was 0.96 ± 0.28 mm. Mean IMT was significantly greater in patients with lower concentrations of F-tes (<10 pg/ml) than in patients with higher concentrations of F-tes (1.03 ± 0.26 vs.0.88 ± 0.23mm, *P*= 0.038.) (Table 2)

3.3. Relationships between Serums Free Testosterone Concentration and Other Variables (Table 3)

A negative correlations were found between serum F-tes concentration and age (r = -0.410, $p < 0.0001$), age at onset (r = -0.277, $p < 0.000$), duration of diabetes (r = -0.171, $p = 0.0104$) and BMI (r = -0.765, $p = 0.0001$) and HbA_{1c} (r = -0.119, $p = 0.0409$). A negative correlations was found between serum F-tes concentration and systolic and diastolic blood pressure (r= -0.601, p= 0.0001, r= -0.457, p= 0.001). Moreover, a negative correlation was found between serum F-tes and total cholesterol concentrations (r = −0.431, p= 0.002). No significant correlation was found between F-test with and triglyceride ($p > 0.05$). Negative correlations was detected between F-tes concentration and mean IMT (r = -0.196, p 0.0093) in men with type 2 diabetes. (Figure 1).

3.4. F-tes Concentrations in Diabetic Retinopathy and Nephropathy

Based on the severity of diabetic retinopathy, serum F-tes concentrations did not differ significantly for patients with NDR, SDR, and PDR (9.8 ± 4.1 vs. 9.7 ± 3.8 vs. 9.5 ± 3.1 pg/ml respectively). Similarly, based on the severity of diabetic nephropathy serum F-tes concentrations did not differ significantly for patients with normoalbuminuria, microalbuminuria, or macroalbuminuria (9.9 ± 4.3 vs. 10.2 ± 4.1 vs. 10.0 ± 3.6 pg/ml, respectively).

Table 1. *Demographic and clinical characteristics of the patients*

Variable	Type 2 diabetes patients (123 men)
Age (years) [mean ± SD]	60.0± 7.9
Age at onset (years) [mean ± SD]	49.0±9.7
Duration of diabetes (years) [mean ± SD]	11.2 ± 7.1
BMI (kg/m^2) [mean ± SD]	29.11 ± 3.41
HbA_{1c}(%)[mean ± SD]	7.5 ±1.6
Systolic blood pressure (mmHg) [mean ± SD]	146.70 ±9.02
Diastolic blood pressure (mmHg) [mean ± SD]	91.76 ±9.36
Total cholesterol (mg/dl) [mean ± SD]	194.84 ±33.20
Triglyceride (mg/dl) [mean ± SD]	151.42 ±15.84
HDL cholesterol (mg/dl) [mean ± SD]	38.38 ± 3.07
Retinopathy (NDR/SDR/PDR) [Number]	68/32/23
Nephropathy [Number] (normoalbuminuria/microalbuminuria/macroalbuminuria)	70/31/22
F-tes (pg/ml) [mean ± SD]	10.6±3.8

BMI, Body Mass Index; Hb, Haemoglobin; HDL, High Density Lipoprotein; NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; IMT, intima-media thickness; F-tes ,serum free testosterone**.**

Table 2. *Carotid duplex measurement of IMT of the patients*

IMT in low F-tes [mean ± SD] mm	IMT in high F-tes [mean ± SD] mm	p
1.03 ±0.26	0.88 ±0.23	0.038

IMT, intima-media thickness

Table 3. *Correlation coefficient between serum testosterone and other variables*

Parameter	*r*	*p*
Age	-0.410	<0.0001
Age at onset	-0.277	<0.0001
Duration of diabetes	-0.171	0.0104
BMI	-0.765	0.0001
HbAlc	-0.119	0.0409
Systolic blood pressure	-0.601	0.0001
Diastolic blood pressure	-0.457	0.001
Total cholesterol	−0.431	0.002
Triglyceride	−0.118	0.414
HDL cholesterol	0.114	0.430
IMT	-0.196	0.0093

BMI, Body Mass Index; HbAlc, Haemoglobin A1c; HDL, High Density Lipoprotein; IMT, intima media thickness

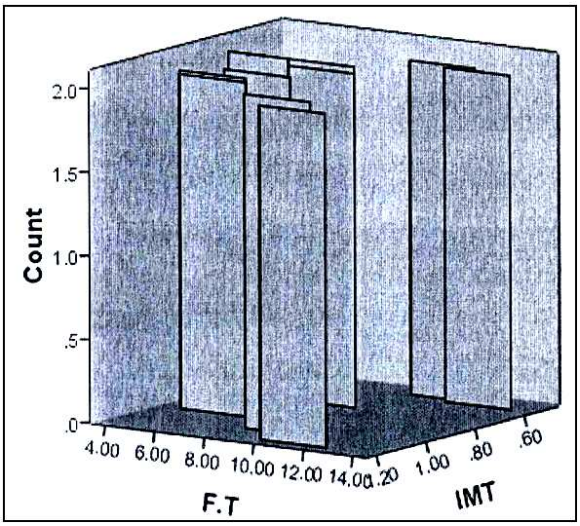

Figure 1. *Correlation between concentration of F-tes and carotid mean IMT*

4. Discussion

In this study we tried to disclose the relationships between serum testosterone concentration and carotid atherosclerosis and its risk factors in men with type 2 diabetes. The relationship between serum testosterone concentration and carotid atherosclerosis was determined by using ultrasonographic measurement of carotid intima media thickness (IMT) in men with type 2 diabetes. Serum F-tes concentrations were negatively correlated with mean IMT. Data revealed that patients with low concentrations of F-tes had greater IMT than those with high concentrations of F-tes. This is found to be in agreement with results of other reports (1, 16, 17, 18, 19). This can be explained by the fact that testosterone is thought to modulate vascular smooth muscle cells (VSMC) through the up regulation of proliferation genes and through possible inhibitory interactions with intracellular signaling pathways induced by pro-inflammatory cytokines, decreasing inflammation-induced apoptosis and promoting proliferation (1, 20).

We revealed a negative correlation between F-tes concentrations and total cholesterol level. This is in agreement with Barud et al and Akinloye et al (21,22) .Other reports stated that testosterone therapy could improve dyslipidemia (23,24). This could be attributed to the fact that cholesterol is the immediate biosynthetic precursor of steroids. Accordingly, low concentrations of testosterone might lead to increased concentrations of cholesterol by changing body fat distribution (25).

Our data showed a negative correlation between serum F-tes concentration and BMI. This was found to be consistent with other reports (22, 23, 24, 26, 27, 28), which confirmed an inverse association between testosterone levels and obesity, increased percentage body fat, insulin resistance and dyslipidemia and trunkal obesity. Moreover, other studies demonstrated that testosterone therapy in obese men reduces body mass index (BMI) and visceral fat mass (29,30).

We searched for the effect of testosterone on glycemic control in diabetic men patients. A relationship between serum concentrations of testosterone with HbA_{1C} level was established. Our result showed a negative correlation between F-tes and HbA1c. This was in agreement with Fukui et al and Jones et al (24, 31) who demonstrated that a benefit on HbA_{1C} of testosterone therapy compared to placebo was observed after 9 months. This can be explained by influences of testosterone on the insulin signaling pathway (32). Testosterone was observed to elevate the expression levels and stimulate translocation of Glut4 in cultured skeletal muscle cells and to upregulate Glut4 by activating insulin receptor signaling pathways in neonatal rats (33). Furthermore, the presence of dyslipedaemia in the body further impairs insulin sensitivity, which is related to insulin resistance (34).

The presence of low free testosterone levels in our patients suggests that testosterone insufficiency may be a risk factor for type 2 diabetes. This is found to be comparable with other studies (35, 36). Men with diabetes have significantly lower plasma concentrations of F-tes than nondiabetic men. This is can be explained by the conversion of testosterone to estradiol by the actions of aromatase in adipose tissue. Therefore, a reduction of testosterone is inevitable with increased expression of aromatase, which is a result of an increased number of adipocytes in diabetic men. In addition, the normal negative feedback regulation of testosterone depends mainly on its aromatization to estradiol. Thus, a high level of aromatization results in the suppression of testosterone secretion. Falling testosterone promotes increasing adipocyte number and fat deposition which gradually leads to a further lowering effect on testosterone levels. In addition, the majority of the normal negative feedback of testosterone on the hypothalamo-pituitary axis occurs via its aromatization to oestradiol (32, 34). Thus, the increased risk for CVD in diabetic men could be partially mediated through low concentrations of testosterone.

Our results displayed a negative correlation between testosterone level and systolic and diastolic blood pressure. This is in agreement with Akinloye et al (22). Explanation of that is the steroid-induced vasodilation mediated via both membrane subpopulations of nuclear steroid receptors, such as the androgen receptor (AR), (36) as well as novel G protein– coupled receptors (38). Chignalia et al presented new evidence on genomic and nongenomic mechanisms of testosterone action on vascular smooth muscle cells in arterial hypertension through modulating associated cellular events (39).

5. Conclusion

In conclusion, serum free testosterone concentration was found to be low in type 2 diabetic men. It has a negative correlation with patients' age, age at onset of the disease, duration of diabetes, BMI and HbA_{1C}, total cholesterol concentration, systolic and diastolic blood pressure and

mean IMT. This may disclose the different mechanisms played by testosterone in the pathogenesis of cardiovascular risk in men with type 2 diabetes.

References

[1] Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. J Endocrinol. 2013a May; 7; 217(3):R47-71.

[2] Channer KS: Endogenous testosterone levels and cardiovascular disease in healthy men. Heart June 2011, 97 (11). 867- 869

[3] Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K,.: Testosterone and Sex Hormone- Binding Globulin Predict the Metabolic Syndrome and Diabetes in Middle-Aged Men. 10.2337/diacare.27.5.1036 Diabetes Diabetes Care. 2004 May;27(5):1036-41.

[4] Mayes JS, Watson GH: Direct effects of sex steroid hormones on adipose tissues and obesity, Obes Rev 2004, 5:197-216.

[5] Kohler TS, Kim J, Feia K, Bodie J, Johnson N, Makhlouf A, et al. Prevalence of androgen deficiency in men with erectile dysfunction. Urology 2008;71: 693-7.

[6] Rezvani MR, Saadatjou SA, Sorouri S, Hassanpour Fard M. Comparison of serum free testosterone, luteinizing hormone and follicle stimulating hormone levels in diabetics and non-diabetics men- a case-control study. J Res Health Sci 2012;12:98-100

[7] Tamler R, Deveney T. Hypogonadism, erectile dysfunction, and type 2 diabetes mellitus: What the clinician needs to know. Postgrad Med 2010;122:165-75

[8] Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 2008;93:1834-40

[9] Soriguer F, Rubio-Martin E, Fernandez D, Valdes S, Garcia-Escobar E, Martin-Nunez GM, et al. Testosterone, SHBG and risk of type 2 diabetes in the second evaluation of the Pizarra cohort study. Eur J Clin Invest 2012;42:79-85

[10] Vangipurapu J, Stančáková A, Kuulasmaa T, Soininen P, Kangas AJ, Ala-Korpela M, Kuusisto J, Laakso M. Association between liver insulin resistance and cardiovascular risk factors. J Intern Med. 2012 Oct;272(4):402-8

[11] Yu Q, Gao F, Ma XL. Insulin says NO to cardiovascular disease. Cardiovasc Res. 2011 Feb; 15; 89(3):516-24.

[12] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2002; 25:S5-S20

[13] Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, Yamakado M: Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet. 2002; 359: 133–135.

[14] Helaly MA[1], Daoud E, El-Mashad N. Does the Serum Testosterone Level Have a Relation to Coronary Artery Disease in Elderly Men? Curr Gerontol Geriatr Res. 2011; 2011: 791765.

[15] Michiaki Fukui. MDJ, Yoshihiro Kitagawa. MDi and Naoto Nakamura, MD2. Association Between Serum Testosterone Concentrationand Carotid Atherosclerosis in Men With Type 2 DiabetesDiabetes Care June 2003; 26 (6) 1869-1873

[16] Fukui M, Kitagawa Y, Nakamura N, Kadono M, Mogami S, Hirata C,. Diabetes Care. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes.2003 Jun; 26(6):1869-73.

[17] Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bonaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med. 2006 Jun; 259(6):576-82.

[18] Firtser S, Juonala M, Magnussen CG, Jula A, Loo BM, et al. Relation of total and free testosterone and sex hormone binding globulin with cardiovascular risk factors in men aged 24–45 years. The Cardiovascular Risk in Young Finns Study. Atherosclerosis 2012; 222: 257–62.

[19] Soisson V, Brailly TS, Empana JP, Feart C, Ryan J, et al. Low plasma testosterone and elevated carotid intima-media thickness: importance of low grade inflammation in elderly men. Atherosclerosis 2012; 223: 244–9.

[20] Nakamura Y, Suzuki T, Igarashi K, Kanno J, Furukawa T, Tazawa C, et al. PTOV1: a novel testosterone-induced atherogenic gene in human aorta. J Pathol. 2006; 209:522-531.

[21] Barud W, Palusiński R, Bełtowski J & Wojcicka G. Inverse relationship between total testosterone and anti-oxidized low density lipoprotein antibody levels in ageing males. Atherosclerosis 2002; 164(2):283-8.

[22] Akinloye O, Blessing Popoola B, Bolanle Ajadi M, Gregory Uchechukwu J, Pius Oparinde D. Hypogonadism and Metabolic Syndrome in Nigerian Male Patients With Both Type 2 Diabetes and Hypertension. Int J Endocrinol Metab. 2014 Jan 1;12(1) :e10749

[23] Heufelder AE, Saad F, Bunck MC, Gooren L, Fifty‐two‐week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl. 2009; 30: 726.

[24] Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011; 34: 828–37.

[25] Brodsky IG, Balagopal P, Nair KS: Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men: a clinical research center study. *J Clin Endocrinol Metab.* 1996; 81:3469– 3475,

[26] Boyanov M, Boneva Z, Christov V. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003; 6: 1–7.

[27] Kapoor D, Goodwin E, Channer K, Jones T. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006; 154: 899–906.

[28] Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, Perelman MA et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care. 2011; 34:1669–1675.

[29] Agledahl I, Hansen JB & Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. Scand J Clin Lab Invest. 2008; 68(7):641-8.

[30] Saad F, Gooren LJ, Haider A & Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. J Androl. 2008; 29(1):102-5.

[31] Fukui M, Tanaka M, Hasegawa G, Yoshikawa T, Nakamura N. Association between Serum Bioavailable Testosterone Concentration and the Ratio of Glycated Albumin to Glycated Hemoglobin in Men with Type 2 Diabetes. Diabetes Care. 2008 Mar;31(3):397-401.

[32] Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol 2013b; 217: R25–45.

[33] Sato K, Iemitsu M, Aizawa K, Ajisaka R. Testosterone and DHEA activate the glucose metabolism‐related signaling pathway in skeletal muscle. Am J Physiol Endocrinol Metab. 2008; 294: E961–8.

[34] 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; 16(1): 146-152.

[35] Keating NL, O'Malley AJ, Smith MR. Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer. J Clin Oncol. 2006; 24(27):4448-56.

[36] Jones TH. Effects of testosterone on Type 2 diabetes and components of the metabolic syndrome. J Diabetes. 2010 ; 2(3):146-56.

[37] Losel RM, Falkenstein E, Feuring M, Schultz A, Tillmann HC, Rossol- Haseroth K, et al. steroid action: controversies, questions, and answers. Physiol Rev. 2003; 83:965–1016.

[38] Pi M, Parrill AL, Quarles LD. GPRC6A mediates the non-genomic effects of steroids. J Biol Chem. 2010; 285:39953–39964.

[39] Chignalia AZ, Schuldt EZ, Camargo LL, Montezano AC, Callera GE, Laurindo FR, et al. Testosterone induces vascular smooth muscle cell migration by NADPH oxidase and c-Src– dependent pathways. Hypertension. 2012;59:1263–1271.