Relationship Between Testosterone Serum Levels and Slow Coronary Flow

Serum Testosteron Düzeyi ve Koroner Yavaş Akım Arasındaki İlişki

Mehmet GÜL,[a]
Burak TANGÜREK,[b]
Hamdi PUSUROĞLU,[a]
Hulusi SATILMIŞOĞLU,[a]
Özgür SURGİT,[a]
Özgür AKGÜL,[a]
Emre AKKAYA,[a]
Ali Kemal KALKAN,[a]
Osman BOLCA,[b]
Abdurrahman EKSİK[a]

[a]Clinic of Cardiology,
Mehmet Akif Ersoy Cardiovascular and Thoracic Surgery Center,
Training and Research Hospital,
[b]Clinic of Cardiology,
Siyami Ersek Cardiovascular and Thoracic Surgery Center,
İstanbul

Geliş Tarihi/*Received:* 16.04.2014
Kabul Tarihi/*Accepted:* 04.09.2014

Yazışma Adresi/*Correspondence:*
Mehmet GÜL
Mehmet Akif Ersoy Cardiovascular and Thoracic Surgery Center,
Training and Research Hospital,
Clinic of Cardiology, İstanbul,
TÜRKİYE/TURKEY
drmg23@gmail.com

ABSTRACT Objective: Slow Coronary Flow (SCF) is a condition related to endothelial dysfunction that is considered within the spectrum of coronary artery disease (CAD). A relationship has been shown to exist between testosterone and CAD. The aim of the study is to investigate the association between the total serum testosterone level and SCF. **Material and Methods:** The study group consisted of 88 male subjects (mean age±55±12 SD: 1 years); 42 of the patients had SCF. The control group had 46 subjects with no significant coronary artery stenosis. Demographic characteristics were same in both groups. Coronary flow rates were determined by the TIMI frame count method. Total testosterone levels were compared between two groups. Testosterone level measurements were performed by radioimmunoassay (RIA) method. **Results:** Mean serum levels of total testosterone were 2.4±0.8 ng/mL in the SCF patients and 2.5±0.9 ng/mL in the control group (p=0.6). No significant association was found between the total testosterone level and TIMI frame count. The age and body mass index (BMI) averages and the frequency of diabetes, dyslipidemia and hypertension were higher in the SCF group than in controls, albeit not at a statistically significant level. Smoking habit was significantly more frequent in the SCF group. **Conclusion:** Even though the serum total testosterone levels seemed to be lower in the SCF patients, no statistically significant difference was found. Our findings are consistent with the known negative effects of cardiovascular risk factors on endothelial function.

Key Words: Coronary angiography; biological markers

ÖZET Amaç: Koroner yavaş akım (KYA), koroner arter hastalığı (KAH) spektrumunda değerlendirilen ve endotel disfonksiyonu ile ilişkili bir klinik durumdur. Testosteronun koroner arter hastalığıyla ilişkisi gösterilmiştir. Bu çalışmanın amacı, serum total testosteron seviyesinin KYA ile olan ilişkisini araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya KAH ön tanısıyla koroner anjiyografi yapılan 42 koroner yavaş akımı olan hasta ve koroner anjiyografisinde anlamlı darlık olmayan 46 kontrol birey olmak üzere toplam 88 erkek hasta (ortalama yaş 55±12 yıl) alındı. KYA grubu ve kontrol grubu hastaları ayni demografik özelliklere sahipti. Koroner akım hızları TIMI frame count (kare sayısı) yöntemi ile belirlendi. KYA saptanan hastalar ve kontrol grubundaki hastaların serum total testosteron seviyeleri karşılaştırıldı. Testosteron seviyeleri radio-immuno-assay (RIA) yöntemiyle ölçüldü. **Bulgular:** Serum total testosteron seviyeleri; KYA grubunda 2,4±0,8 ng/ml kontrol grubunda 2,5±0,9 ng/ml olarak tespit edildi (p:0,6). Total testosteron düzeyleri ile TIMI frame count arasında anlamlı bir korelasyon gösterilemedi. KYA grubunda yaş ve beden kitle indeksi (BKİ) ortalamaları ile diyabet sıklığı, dislipidemi ve hipertansiyon oranları istatistiksel olarak anlamlı düzeyde olmamakla beraber daha yüksek bulundu. Sigara içimi KYA grubunda anlamlı düzeyde fazlaydı. **Sonuç:** Serum total testosteron seviyeleri KYA hasta gurubunda daha düşük saptanmasına rağmen istatistiksel olarak anlamlı bir ilişki bulunamadı. Bulgularımız kardiyovasküler risk faktörlerinin endotel disfonksiyonu üzerindeki negatif etkileriyle uyumludur.

Anahtar Kelimeler: Koroner anjiyografi; biyolojik belirteçler

Turkiye Klinikleri J Cardiovasc Sci 2014;26(2):79-84

Slow coronary flow (SCF) is characterized by delayed contrast dye opacification without significant stenosis of epicardial coronary arteries. Most patients with SCF are debilitated with recurrent chest pain, commonly resulting in repeated hospital admissions.[1] Several mechanisms have been proposed for etiology of SCF, including microvascular and endothelial dysfunction, small-vessel disease and diffuse atherosclerosis.[2,3] It has more recently been shown that the coronary arteries of an important proportion of SCF patients present intimal thickening, diffuse calcification, or atheromatous plaques that do not cause irregularity of the lumen. Based on this finding, it would be appropriate to consider SCF that was formerly thought as a subgroup of cardiac syndrome X , as a coronary artery disease.[4]

Androgen levels below or above the physiologic limits associated with cardiovascular disease.[5-7] Especially, exogenous synthetic androgens associated with adverse cardiovascular event and impaired lipid parameters. Effects of androgen deficiency has been known better. Epidemiology studies showed that low testosterone levels help the progression of atherosclerotic change.[7] There are reports regarding correlation between low testosterone levels and cardiovascular risk factors such as human atherogenic lipid profile, systolic and diastolic hypertension, obesity and high fibrinogen levels.[8-11] Considering the effect of testosterone on the cardiovascular system and the lipid profile, one can hypothesize a relationship between testosterone levels and SCF. However, the relation between SCF and serum testosterone levels has not been investigated previously. The objective of this study was to investigate the relationship between total testosterone serum level and SCF.

MATERIAL AND METHODS

The study included 42 consecutive male patients (mean age 57.1±14.6 years) with angiographically normal but with SCF in coronary arteries. The control group consisted of 46 consecutive male patients (mean age 53.9±12.1 years) with angiographically normal coronary arteries without SCF. Coronary flow rates were determined by the TIMI frame count method. Subjects with a history of hypogonadism or use of a drug that affects sexual hormone levels (for example, anti-androgens for prostate cancer) were excluded from the study. Patients with a history of congestive heart failure, coronary artery disease including spasm, plaque, or ectasia, chronic obstructive pulmonary disease, valvular heart disease, hyperthyroidism, ventricular preexcitation, atrioventricular conduction abnormalities and those taking medications known to alter cardiac conduction were excluded from the study. The total serum testosterone levels of the SCF patients were compared to those of the healthy subjects. Approval of the study protocol was obtained from the local ethics committee and informed consent was obtained from all of the participants.

Subjects with systolic blood pressure higher than 140 mmHg or diastolic pressure over 90 mmHg, and those with a history of antihypertensive drug use were considered to be hypertensive. Subjects whose fasting LDL level was higher than 130 mg/dL and those with a history of statin use were considered as hypercholesterolemic, while those with a fasting triglyceride level above 150 mg/dL were classified as hypertriglyceridemic. Finally, subjects whose fasting blood glucose exceeded 126 mg/dL, or treated with the diagnosis of diabetes mellitus, were accepted as diabetic. Smoking history was also recorded.

SLOW CORONARY FLOW DIAGNOSIS

Selective coronary angiography was performed by means of the Judkins technique in multiple projections. We used iohexol (Omnipaque) as contrast agent during coronary angiography in all patients and control subjects. An injection of 5-8 ml contrast medium was given manually at each position. Coronary angiograms were analyzed by cardiologists blinded to the patients' data. Coronary flow rates of all subjects were determined by the TIMI frame count (TFC) method. Coronary blood flow was measured quantitatively using the TIMI frame count which was derived from the number of cineframes recorded from the first entrance of contrast to its arrival at the distal end of either the left anterior descending artery (LAD), circumflex artery

(Cx), or right coronary artery (RCA).[12] Arteriographies were recorded at a rate of 30 frames/sec. Initial frame count is defined as the frame in which concentrated dye occupies the full width of proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. The distal reference points were the terminal bifurcations of the LAD and Cx, and the first side-branch of the posterolateral artery in the RCA. Available measurements showed that the length of LAD is on the average 1.7 times longer than that of RCA and Cx, the frame count for LAD is divided into 1.7 to obtain the corrected LAD (cLAD) frame count. According to data obtained from subjects with normal coronaries, the TFC is 36.2±2.6 for LAD, 22.2±4.1 for Cx, and 20.4±3.0 for RCA. The patients who had TFCs greater than the predicted normal values were regarded as to have SCF.

BLOOD SAMPLES

For each participant, blood samples were drawn from an antecubital vein before the coronary angiography after a 12-hour overnight fasting. Total testosterone levels were measured by radioimmunoassay (RIA) using a Testosterone TIA CT kit by Biosource Europe (Belgium).

STATISTICAL ANALYSIS

Data entry and statistical analysis was performed using SPSS 11.5. Normally distributed continuous variables were compared by Student's t-test and for other variables by the Mann-Whitney U test. Categorical variables were compared by the chi-squared test. A p-value of less than 0.05 was accepted as significant.

RESULTS

Clinical and demographic characteristics of the patients with SCF and control group were presented in Table 1. The ages of slow coronary flow patients (57.1±14.6) were similar to those of the control group (53.9±12.1). There were no statistically significant differences between the groups regarding body mass index (BMI).

TABLE 1: Comparison of the clinical and demographic characteristics of slow coronary flow in the patients and the control group.

	SCF (n=42)	Controls (n=46)	p-value
Age (years)	57.1±14.6	53.9±12.1	0.5
BMI (kg/m²)	28.3±2.8	27.7±2.7	0.6
Testosterone (ng/mL)	2.4±0.8	2.5±0.9	0.6
Dyslipidemia, n	14 (33)	10 (21.7)	0.4
Diabetes, n	19 (45.2)	12 (26.1)	0.06
Hypertension, n	22 (52.4)	18 (39.1)	0.7
Smoking, n	26 (61.9)	14 (30.4)	0.003

Data were given as mean ±SD or as n (%); SCF: Slow coronary flow.

Hypertension and dyslipidemia frequencies, two of the risk factors for coronary artery disease, were similar in two groups; no statistically significant differences were noted. The frequency of smoking was significantly higher in the SCF group (61.9%) than in the control group (30.4%), (p=0.003). Although the frequency of diabetes mellitus in the SCF group (45.2%) was higher than the control group (26.1%), statistically significant difference was not reached (p: 0.06). The mean serum total testosterone levels were 2.4±0.8 ng/mL in the SCF patients and 2.5±0.9 ng/mL in the control group. The difference between the groups was not statistically significant (Table 1).

The TIMI frame count of slow coronary flow and control groups were presented in Table 2. The TIMI frame count for all the epicardial coronary arteries were significantly higher in the SCF group than in the control group ($p<0.01$). No correlation was noted between the total cholesterol levels and TIMI frame count of any epicardial coronary artery in the SCF and the control groups (Table 2).

DISCUSSION

We found a lower total testosterone level in the SCF patients as compared to the control group, without statistical difference. The frequency of smoking was significantly higher in the SCF group and the higher frequency of diabetes was remarkable but not statistically significant. These findings are compatible with the known negative effects of cardiovascular risk factors on endothelial function.

TABLE 2: TIMI frame count of patients in the slow coronary flow and control groups.

	Slow Coronary Flow (n=42)	Control Group (n=46)	p-value
Left Anterior Descending (LAD) artery	82±23	35±6	<0.01
Corrected LAD TMI frame count (cLAD)	48±14	21±4	<0.01
Circumflex artery (Cx)	40±12	22±4	<0.01
Right Coronary Artery (RC)	38±13	21±5	<0.01

Data were presented as mean ±SD.

The underlying mechanism of late opacification in the epicardial coronary arteries without stenosis observed in SCF has yet to be elucidated. The histopathological characteristics are similar to those of coronary atherosclerosis and microvascular dysfunction. Diffuse calcification, diffuse intimal thickening and parietal atheromatous plaques, which, however, do not restrict the lumen, have been found along the epicardial coronary arteries of certain SCF patients.[13,14] As indicated by these pathogenetic processes, the presence of ischemia and its clinical expression, angina, is inevitable. Metabolic processes such as myocardial lactate production and oxygen consumption; stress electrocardiography and thallium-201 myocardial perfusion scintigraphy confirmed the presence of ischemia in 30-80% of these patients.[15]

Testosterone, which is present in larger quantities than any other androgens, may be regarded as the most important testicular hormone. Testosterone and all other androgens are steroidal compounds. Androgens are synthesized both in the testes and the adrenal glands, either from cholesterol or directly from acetyl coenzyme A. The serum testosterone levels range between 250 and 1,200 ng/dL (2.5-12 ng/mL) in the healthy adult males, decreasing with age.[16] Total testosterone serum levels were in the age-adjusted normal range, both in the SCF and the control groups.

Hu et al. showed that middle-aged male patients with coronary artery disease (CAD) present a lower level of serum testosterone and the testosterone level was negatively correlated with the severity of coronary artery stenosis.[17] There was a significant correlation between angiographic Gensini score and testosterone level. In an another observational study by Shores et al. testosterone treatment in a cohort of men with low testosterone levels, was associated with decreased mortality compared with no treatment. Also there was no significant effect modification found by age, diabetes, or coronary heart disease.[18] Arbel et al showed that current smoking was the most significant variable related to SCF and the SCF group included significantly more smokers (41% versus 15%, p = 0.002) in their study.[19] In our study, the frequency of smoking was significantly higher in the SCF group than in the control group. It has been clearly demonstrated that inflammation plays an important role in the initiation, development, and evolution of atherosclerosis, suggesting that atherosclerosis is an inflammatory disease.[20,21] There are many inflammation markers studied in SCF. Kalay et al. showed that patients with SCF have significantly increased red blood cell distribution width (RDW) and serum uric acid levels.[22] Akpınar et al. demonstrated increased RDW and platelet distribution width (PDW) in SCF patients may cause microvascular blood flow resistance due to impaired cell deformability.[23]

The association of endothelial dysfunction and androgen deficiency is supported by pre-clinical and clinical studies.[24] Testosterone is reported as having a favorable effect on the endothelial function, as shown e.g. by the brachial artery vasoreactivity in the male CAD patients.[25] Clinical studies also indicate that testosterone has positive effects in cardiovascular disease. Malkin et al. reported that testosterone might be a protective factor against atherosclerosis; men with low testosterone levels have an increased risk of CAD.[26,27] The authors suggest that immune modulating properties of testosterone mediate atheroma inhibition, thus opposing acute coronary ischemia.[28] English et al

recorded the positive outcome of testosterone administration in exertion-induced myocardial ischemia, measured by the time to ST-segment depression at a stress ECG; the authors suggested that androgen therapy might mediate vasodilatation.[29] Testosterone may have a protective action on the vessels by modulating cardiovascular risk factors, mainly hypertension, high cholesterol levels, diabetes and obesity.[30-32] Low levels of total and free testosterone seem to correlate with an increase in aortic atherosclerosis in the elderly males.[33] Hypogonadism is hypothesized to play a role in the cardiovascular death risk (CVD) through metabolic syndrome.[34] Shores et al showed that dihydrotestosterone had a nonlinear association with stroke risk in which there was an optimal DHT level associated with the lowest stroke risk.[35] Androgen deficiency is associated with increased levels of total cholesterol, low-density lipoprotein, increased production of proinflammatory factors, and increased thickness of the arterial wall and contributes to endothelial dysfunction. Testosterone supplementation restores arterial vasoreactivity, reduce proinflammatory cytokines, total cholesterol, and triglyceride levels and also improve endothelial functions. But it might reduce high-density lipoprotein levels.[36] Testosterone level inversely correlates with those of insulin, fibrinogen and plasminogen activator inhibitor-1 (PAI-1), as reported by Philips et al. in patients diagnosed with ischemic heart disease.[37] This leads to the hypothesis that testosterone deficiency due to age and obesity may increase coagulability, thus preparing the ground for atherosclerotic development.

As indicated by the cited reports and considering the undesirable effects of abnormal testosterone levels on the cardiovascular system and the lipid profile, such abnormal testosterone levels could be responsible for SCF. This hypothesis is yet untested; existing reports examined the total and free testosterone levels and we studied the total testosterone level.

Limitations of the study: Small number of patients involved in this study; free testosterone, or simultaneously free and total testosterone, could have been measured. The medication use of the patients in both groups was not evaluated. The effects of these medications on the coronary blood flow were not assessed. On the other hand, the patients' risk factors such as hypertension, diabetes mellitus, and hyperlipidemia, were similar and the medications that they used were alike in general. We did not assess other laboratory markers such as insulin levels, C reactive protein, other inflammation markers.

CONCLUSION

Even though the serum total testosterone level appeared to be lower in the SCF patients, no statistically significant association was found. Statistical significance might potentially be reached in the studies with higher number of cases or if free testosterone level measurements are obtained. Our findings are consistent with the known negative effects of cardiovascular risk factors on the endothelial function.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. Am Heart J 1972;84(1):66-71.
2. Kurtoglu N, Akcay A, Dindar I. Usefulness of oral dipyridamole therapy for angiographic slow coronary artery flow. Am J Cardiol 2001;87(6):777-9, A8.
3. Goel PK, Gupta SK, Agarwal A, Kapoor A. Slow coronary flow: a distinct angiographic subgroup in syndrome X. Angiology 2001;52 (8):507-14.
4. Sullivan ML, Martinez CM, Gennis P, Gallagher EJ. The cardiac toxicity of anabolic steroids. Prog Cardiovasc Dis 1998;41(1):1-15.
5. Kamischke A, Heuermann T, Krüger K, von Eckardstein S, Schellschmidt I, Rübig A, et al. An effective hormonal male contraceptive using testosterone undecanoate with oral or injectable norethisterone preparations. J Clin Endocrinol Metab 2002;87(2): 530-9.
6. Kayaalp SO. [Skin]. Akılcı Tedavi Yönünden Tıbbi Farmakoloji, 2. 9. Baskı. Ankara: Hacettepe-Taş Yayıncılık; 2000. p.1376-7.
7. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002;87(8): 3632-9.

8. Phillips GB, Jing TY, Resnick LM, Barbagallo M, Laragh JH, Sealey JE. Sex hormones and hemostatic risk factors for coronary heart disease in men with hypertension. J Hypertens 1993;11(7):699-702.
9. Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, et al. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J Clin Endocrinol Metab 1990;71(4):929-31.
10. Glueck CJ, Glueck HI, Stroop D, Speirs J, Hamer T, Tracy T. Endogenous testosterone, fibrinolysis, and coronary heart disease risk in hyperlipidemic men. J Lab Clin Med 1993; 122(4):412-20.
11. Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab 1997;82(2): 682-5.
12. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93 (5):879-88.
13. Pekdemir H, Cin VG, Çiçek D, Camsari A, Akkus N, Döven O, et al. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. Acta Cardiol 2004;59(2):127-33.
14. Cin VG, Pekdemir H, Camsar A, Ciçek D, Akkus MN, Parmaksýz T, et al. Diffuse intimal thickening of coronary arteries in slow coronary flow. Jpn Heart J 2003;44(6):907-19.
15. Yaymaci B, Dagdelen S, Bozbuga N, Demirkol O, Say B, Guzelmeric F, et al. The response of the myocardial metabolism to atrial pacing in patients with coronary slow flow. Int J Cardiol 2001;78(2):151-6.
16. Ganong WF. The adrenal medulla & adrenal cortex. Review of Medical Physiology. 16th ed. London: Prentice Hall International Inc; 1993. p.391-4.
17. Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X, et al. Low testosterone level in middle-aged male patients with coronary artery disease. Eur J Intern Med 2011;22(6):e133-6.
18. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97(6):2050-8.
19. Arbel Y, Rind E, Banai S, Halkin A, Berliner S, Herz I, et al. Prevalence and predictors of slow flow in angiographically normal coronary arteries. Clin Hemorheol Microcirc 2012;52(1):5-14.
20. Gul M, Uyarel H, Ergelen M, Karacimen D, Ugur M, Turer A, et al. The relationship between red blood cell distribution width and the clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: a 3-year follow-up. Coron Artery Dis 2012;23(5):330-6.
21. Gul M, Kalkan AK, Uyarel H. Serum bilirubin: a friendly or an enemy against cardiovascular diseases? J Crit Care 2014;29(2):305-6.
22. Kalay N, Aytekin M, Kaya MG, Ozbek K, Karayakalı M, Söğüt E, et al. The relationship between inflammation and slow coronary flow: increased red cell distribution width and serum uric acid levels. Turk Kardiyol Dern Ars 2011;39(6):463-8.
23. Akpinar I, Sayin MR, Gursoy YC, Aktop Z, Karabag T, Kucuk E, et al. Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon. J Cardiol 2014;63(2):112-8.
24. Foresta C, Zuccarello D, De Toni L, Garolla A, Caretta N, Ferlin A. Androgens stimulate endothelial progenitor cells through an androgen receptor-mediated pathway. Clin Endocrinol (Oxf) 2008;68(2):284-9.
25. Kang SM, Jang Y, Kim Ji, Chung N, Cho SY, Chae JS, et al. Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. Am J Cardiol 2002;89(7):862-4.
26. Malkin CJ, Morris PD, Pugh PJ, English KM, Channer KS. Effect of testosterone therapy on QT dispersion in men with heart failure. Am J Cardiol 2003;92(10):1241-3.
27. Malkin CJ, Pugh PJ, Jones RD, Jones TH, Channer KS. Testosterone as a protective factor against atherosclerosis--immunomodulation and influence upon plaque development and stability. J Endocrinol 2003;178(3):373-80.
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):3313-8.
29. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000;102(16):1906-11.
30. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. Cardiovasc Res 2002;53(3):688-708.
31. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL; Rancho Bernardo Study. 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.
32. Haffner SM, Karhapää P, Mykkänen L, Laakso M. Insulin resistance, body fat distribution, and sex hormones in men. Diabetes 1994;43 (2):212-9.
33. Jones RD, Malkin CJ, Channer KS, Jones TH. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: further supportive data. J Clin Endocrinol Metab 2003;88(3):1403-4;author reply 1404.
34. Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl 2009;30(1):10-22.
35. Shores MM, Arnold AM, Biggs ML, Longstreth WT Jr, Smith NL, Kizer JR, et al. Testosterone and dihydrotestosterone and incident ischaemic stroke in men in the Cardiovascular Health Study. Clin Endocrinol (Oxf) 2014 Mar 19. doi: 10.1111/cen.12452.
36. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009;30(5):477-94.
37. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb 1994;14(5):701-6.