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ANDROLOGY

Original Article

The relationship between lipoprotein-associated phospholipase A2 with cardiovascular risk factors in testosterone deficiency

Testosteron eksikliğinde lipoprotein ilişkili fosfolipaz A2'nin kardiyovasküler risk faktörleriyle ilişkisi

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ABSTRACT

Objective: Lipoprotein-associated phospholipase A2 (Lp-PLA2) which is believed to play a role in atherosclerotic inflammatory process due to its function in hydrolysis of phospholipids and release of pro-inflammatory products, is considered as a novel biomarker for vascular risk. In this study we aimed to investigate the alterations in Lp-PLA2 and its relationship with other cardiovascular risk factors in patients with testosterone deficiency.

Material and methods: Forty hypogonadic male and 30 healthy male aged between 18-50 years were enrolled in this study. Height-weight, waist-to-hip circumference, body mass index (BMI) blood pressure, and body fat measurements were performed in all subjects. Blood glucose, albumin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, high sensitive C-reactive protein (hs-CRP), apo-A1, apo-B, fibrinogen, insulin, total testosterone, sex hormone binding globulin (SHBG), small dense low-density lipoprotein (sd-LDL), paraoxonase 1, oxidized low-density lipoprotein (ox-LDL) and Lp-PLA 2 values were measured. Free and bioavailable testosterone levels were calculated. Data management was carried out with the statistical program SAS Version 9.2. Statistical evaluations were performed using Analysis of Variance (ANOVA), Kruskal-Wallis test, Wilcoxon test, correlation analysis and chi-square analysis. P values <0.05 were considered statistically significant.

Results: In patients with hypogonadism, significant increase in Lp-PLA2 levels were accompanied with risk factors of atherosclerosis, such as increase in total cholesterol, apo-B, sd-LDL, weight, BMI, body fat percentage, and decrease in paraoxonase 1 levels. Although the differences were not significant, similarly ox-LDL, hs-CRP, triglyceride, LDL-cholesterol levels were found to be higher in patients with hypogonadism compared to the control group. The mean level of Lp-PLA2 was the highest when compared with the group of secondary hypogonadism with the lowest testosterone level.

Conlusion: Our study has demonstrated that the testosterone deficiency increases cardiovascular risk via its effects on lipid metabolism and Lp-PLA2 can be used to assess this risk.

Keywords: Cardiovascular system; hypogonadism; phospholipases A2.

ÖZ

Amaç: Fosfolipidleri hidrolize ederek proinflamatuar ürünleri açığa çıkartmasından dolayı aterosklerotik inflamatuvar süreçte rol aldığı düşünülen Lipoprotein ilişkili Fosfolipaz A2 (Lp-PLA2) son yıllarda yeni bir vasküler risk biyobelirteci olarak kabul edilmektedir. Bu çalışmada testosteron eksikliğinde Lp-PLA2'nin değişimi ve diğer kardiyovasküler risk faktörleriyle ilişkisini araştırdık.

Gereç ve yöntemler: Çalışmaya 18-50 yaşları arasındaki 40 hipogonadizm tanılı erkek ve aynı yaş grubundaki 30 sağlıklı erkek dahil edildi. Hastaların boy-kilo, bel-kalça çevresi, vücut kitle indeksi (VKİ) kan basıncı ve vücut yağ oranı ölçümleri kaydedildi. Serum glukoz, albumin, total kolesterol, HDL-kolesterol, LDL-kolesterol, trigliserid, yüksek duyarlı C-reaktif protein (hs-CRP), apo-A1, apo-B, plazma fibrinojen düzeyi, açlık insülin düzeyi, total testosteron, SHBG, sd-LDL, Paraoksonaz 1, ox-LDL ve Lp-PLA 2 değerleri ölçüldü. Serbest ve biyokullanılabilir testosteron düzeyleri hesaplandı. İstatistiksel analiz için SAS Version 9,2 kullanıldı. İstatistiksel değerlendirmeler Varyans Analizi (ANOVA), Kruskal-Wallis testi, Wilcoxon testi, korelasyon analizi ve ki-kare testi kullanılarak gerçekleştirildi. P<0,05 düzeyi istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hipogonadizm olgularında anlamlı Lp-PLA2 yüksekliğine total kolesterol, apo-B, sd-LDL, VKİ, vücut yağ oranı yüksekliği ve paraoksonaz 1 düşüklüğü gibi arteroskleroz risk faktörlerinin eşlik ettiği görüldü. Benzer şekilde hipogonadizmli hastalarda istatistiksel olarak anlamlı farklılık saptanmasa da, ox-LDL, hs-CRP, trigliserid, LDL-kolesterol düzeyleri kontrol grubuna göre yüksek saptandı. Testosteron düzeyi en düşük olan sekonder hipogonadizm grubunun, Lp-PLA2 ortalaması diğer gruplara göre en yüksek değerlere sahipti.

Sonuç: Çalışmamızın bulguları, erkeklerde testosteron eksikliğinin lipid metabolizması üzerine olan etkileri yoluyla kalp damar hastalığı riskini arttırdığını ve bu riskin belirlenmesinde Lp-PLA2'nin kullanılabileceğini gösterdi.

Anahtar Kelimeler: Kardiyovasküler sistem; hipogonadizm; fosfolipaz A2.

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Introduction

Nowadays, mortality linked to cardiovascular (CV) events ranks first among all mortality causes.[1] There is strong evidence that androgen deficiency is associated with atherosclerosis.[2] Attention has been paid to the relationship between androgenic hormones and cardiovascular system (CVS) after the observation that rates of CV mortality, thrombogenic events.[4] increase with diethylstilbestrol (DES)[3] which is used in prostate cancer treatment.

It has been reported that androgen deficiency promotes processes leading to atherosclerosis such as oxidative stress, endothelial dysfunction and proinflammatory factors by affecting lipid profile and all of the components of the metabolic syndrome accompany hypogonadism, but cause and effect relationship between androgen deficiency and these circumstances has not been clarified yet. Testosterone level has been shown to be significantly low in patients with cardiovascular disease relative to healthy men.[5] Norfolk European Prospective Cancer Investigation Study, monitoring 11.606 men, showed that CVS- mortality was inversely correlated with testosterone levels.[6] The high prevalence of hypogonadism in men with coronary artery disease has urged the analysis of relations between cardiovascular risk factors and low testosterone levels. Researchs have shown the effectiveness of vascular inflammatory entities like insulin resistance, central obesity and dyslipidemia which are proatherogenic conditions and suggested that testosterone replacement improved these disorders.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) which is believed to play a role in atherosclerotic inflammatory process due to its function in hydrolysis of phospholipids and release of pro-inflammatory products, is considered as a novel predictive biomarker for vascular risk.

In this prospective and randomized study, we aimed to show whether Lp-PLA2 takes part in vascular inflammation seen in testosterone deficiency and determine the relationship between Lp-PLA2 and proatherogenic conditions associated with testosterone deficiency and other cardiovascular risk factors. There is no published research on the relationship between testosterone deficiency and Lp-PLA2 yet. The mean level of Lp-PLA2 in cases with testosterone deficiency was relatively higher when compared with the group of secondary hypogonadism with the lowest testosterone level.

Material and methods

Patients

Study groups consisted of 40 hypogonadic and 30 healthy men aged between 18-50 years. All patients were clinically assesed by detailed history (including age, metabolic, endocrinological, cardiovasvular, renal, hepatic or inflammatory diseases, medication) and physical examination. The study was performed in compliance with the Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects*. The subjects were all informed about the study protocol and their informed consent was obtained. Hypogonadic patients consisted of cases with primary (n=25) and secondary (n=15) hypogonadism.

Patients with a history of hypogonadism for at least five years and total testosterone levels below 12 nmol/L (3.46 ng/mL) were included in Group 1. Healthy men with total testosterone levels higher than 12 nmol/L (3.46 ng/mL) without any known disease, whose age distribution was consistent with the study group were included in Group 2.

Patients with metabolic and endocrinological disorders, cardiovascular disease, renovascular and secondary hypertension, malignant diseases, primary liver disease, kidney failure, inflammatory diseases not related to hypogonadism and receiving androgen, lipid lowering, antiplatelet therapy in the previous three years were excluded from the study group. Study participants using on chronic drug therapy were excluded from the control group. The study was performed in compliance with the Declaration of Helsinki. Ethics committee approval was received for this study from the ethics committee of Ege University Faculty of Medicine.

Measurements for body height-weight, waist-to-hip circumference, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressures and body fat percentage were performed. Bioelectricity impedance method was used for body fat ratio measurement (Omron BF-508, Omron Healthcare, Kyoto, Japan).

Blood sampling

Blood samples were drawn from each participant following an overnight fasting of 12 hours before 10AM. Venous blood samples were drawn into serum separator gel tubes and anticoagulant tube and were centrifuged 3000 g for 10 minutes. Biochemical tests on serum samples; glucose, apoA-1, apoB, albumin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, sensitive CRP, insülin, total testosterone levels and fibrinogen levels in plasma samples were measured within the day the samples were drawn. Sera for SHBG, PON 1, sd-LDL, ox-LDL and Lp-PLA2 measurements were stored at -80°C until the time of analysis.

Laboratory investigation

Serum fasting glucose, albumin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, hs-CRP and apo-

A1 and apo-B levels were measured in the Cobas c 502 and Cobas c 702 modular analyzers (Roche Diagnostics GmbH, Mannheim, Germany), serum total testosterone levels and SHBG levels were measured in the Cobas e 602 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany), plasma fibrinogen and serum insulin levels were measured in the BCS XP (Siemens Healthcare Diagnostics, Marburg, Germany) and IMMULITE 2000 (Siemens Healthcare Diagnostics, Marburg, Germany) and Cobas e 602 (Roche Diagnostics GmbH, Mannheim, Germany). ox-LDL and Lp-PLA2 were measured by ELISA method (Immundiagnostic, Bensheim, Germany and PLAC®, diaDexus Inc., South San Francisco, USA, respectively).

After the precipitation process[7], sd-LDL was measured in Cobas c 502 system by colorimetric enzymatic direct LDL method (Roche Diagnostic GmbH, Mannheim, Germany) and Paraoxonase 1 was measured by spectrophotometric method.[8]

Free and bioavailable testosterone were calculated from the web address "http://www.issam.ch/freetesto.htm" by using total testosterone, SHBG and albumin levels[9], HOMA-IR index and QUICKI index were calculated from the web addresses https://sasl.unibas.ch/11calculators-HOMA.php[10] and "https://sasl.unibas.ch/11calculators-QUICKI.php[11], respectively.

Statistical analysis

Statistical program SAS Version 9.2 was used for data management. Statistical evaluations were performed using Analysis of Variance (ANOVA), Kruskal-Wallis test, Wilcoxon test, correlation analysis and chi-square analysis. Two tailed p values <0.05 were considered statistically significant.

Results

The mean values for body weight (p=0.0332), BMI (p=0.0089), hip circumference (p=0.0020) and body fat ratio (p=0.0259) of hypogonadic male were significantly higher than the control group. Statistically significant difference was not detected between the groups with regard to waist/hip ratio, waist circumference, SBP, DBP and smoking rates (Table 1).

The mean values for total cholesterol (p=0.0217), apo-B (p=0.0048), Lp-PLA 2 (p=0.0386) and sd-LDL (p=0.0089) of the patients were significantly higher than the control group, while mean values of paraoxonase-1 were significantly lower (p=0.0001). There was no statistically significant difference between the case and control groups with regard to fasting glucose, hs-CRP, fibrinogen, HDL-cholesterol, LDL-cholesterol, triglycerides, apo-A1, fasting insulin, HOMA-IR, QUICKI and ox-LDL values (Table 2).

Table 1. Demographic and clinical data of all cases and the control group

	Patients (n=40) Mean±SD	Control (n=30) Mean±SD	p
Age (year)	34.15±6.38	35.23±7.88	0.3931
Weight (kg)	84.80±12.36	80.53±11.10	0.0332*
Height (cm)	175.28±6.43	176.30±5.87	0.6777
BMI (kg/m^2)	27.57±3.54	25.76±3.46	0.0089*
Waist circumference (cm)	95.05±10.17	92.10±9.44	0.0856
Hip circumference (cm)	104.70±7.69	100.23±6.65	0.0020*
WC/HC	0.91±0.07	0.92±0.05	0.6294
SBP (mmHg)	116.05±9.74	114.67±9.07	0.5132
DBP (mmHg)	70.95±10.80	74.70±9.34	0.1937
Body fat ratio (%)	24.41±6.89	21.74±6.56	0.0259*
Smoking (n/%)	21/52.5	15/50	>0.05

*Significant p values with "linear contrast" depending on the variance analysis. Group 1: Primary hypogonadism cases, Group 2: Secondary hypogonadism cases, Group 3: Healthy controls. SD: standard deviation; BMI: body mass index; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure

In this study, patients with secondary hypogonadism who had the lowest testosterone levels had the highest fibrinogen levels, though not statistically significant (p=0.17). In addition, fibrinogen was positively correlated with hs-CRP (p=0.62). The secondary hypogonadism group with the highest Lp-PLA2 and the lowest testosterone level (p=0.06), had the highest ox-LDL (p=0.09), hs-CRP (p=0.0297), and LDL-cholesterol levels (p=0.0101).

Correlation analysis

There was significant correlation between total testosterone and BMI (r=-0.338, p=0.033), hip circumference (r=-0.318, p=0.045), body fat ratio (r= -0.446, p=0.004), levels of total cholesterol (r=-0.371, p=0.019), LDL-cholesterol (r=-0.3225, p=0.042) and apo-A1 (r=0.326, p=0.04), also between Lp-PLA 2 and hs-CRP (r=-0.344, p=0.03) and fibrinogen (r=-0.378, p=0.016) in case group.

Discussion

In this study, there was a negative correlation between total testosterone and body weight, BMI, body fat percentage, total cholesterol, and LDL-cholesterol levels, whereas, there was a positive correlation between free and bioavailable testosterone and a lower number of metabolic syndrome components in the case group. This signified that total testosterone could better predict the risk of metabolic syndrome compared to free and bioavailable testosterone.

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Table 2. Biochemical data of all cases and the control group (mean ± SD of the data having normal distribution and median (min-max) values of data having abnormal distribution were used)

	Patients (n=40) Median (min-max)	Control (n=30) Median (min-max)	p
Total Testosterone (ng/mL)	2.51 (0.03-3.39)	5.00 (3.76-10.75)	0.00001**
Free Testosterone (pg/mL)	56.40 (0.90-85.80)	100.20 (73.20-189.00)	0.00001**
Bioavailable Testosterone (ng/mL)	1.40±0.62	2.76±0.65	0.00001*
SHBG (nmol/L)	19.79 (7.22-57.26)	30.56 (18.04-59.95)	0.00001**
Fasting blood glucose (mg/dL)	87.80±12.44	89.03±9.37	0.6613
Fasting Insulin (mIU/mL)	8.67 (2.00-42.40)	8.24 (2.00-22.70)	0.4335
HOMA-IR	1.88 (0.41-9.53)	2.14 (0.35-5.16)	0.8262
QUICKI	0.35 (0.28-0.45)	0.34 (0.30-0.46)	0.7977
Total Cholesterol (mg/dL)	193.03±36.57	175.13±30.43	0.0217*
LDL-cholesterol (mg/dL)	117.98±29.67	106.53±26.91	0.0541
HDL-cholesterol (mg/dL)	42.45±11.08	44.33±10.16	0.4236
Triglycerides (mg/dL)	132.00 (43.00-445.00)	105.50 (34.00-333.00)	0.1510
Apo-A 1 (mg/dL)	131.03±18.61	130.94±17.36	0.8737
Apo-B (mg/dL)	100.98±26.19	85.97±18.59	0.0048*
hs-CRP (mg/dL)	0.21 (0.01-1.45)	0.09 (0.02-0.97)	0.0999
Fibrinogen (mg/dL)	323.00±71.60	324.33±67.87	0.9661
Lp-PLA 2 (ng/mL)	242.70±49.10	221.68±41.78	0.0386*
ox-LDL (ng/mL)	47.37 (0.10-524.58)	43.02 (0.24-708.53)	0.5212
sd-LDL (mg/dL)	27.00 (8.00-68.00)	18.00 (8.00-46.00)	0.0089**
Paraoxonase-1 (U/L)	52.35±13.25	69.74±12.14	0.0001*

*Linear contrast depending on variance analysis, **Two independent samples Wilcoxon test. Group 1: Primary hypogonadism cases, Group 2: Secondary hypogonadism cases, Group 3: Healthy controls. £: The result of a patient was excluded from the statistical evaluation because it was not in the range of ox-LDL measurement. SHBG: sex hormone binding globulin; HOMA-IR: homeostatic model assessment for insulin resistance; QUICKI: quantitative insulin-sensitivity check index; Apo-A 1: apolipoprotein A 1; Apo-B: apolipoprotein B; hs-CRP: high-sensitivity C-reactive protein; Lp-PLA 2: lipoprotein-associated phospholipase A2; ox-LDL: oxidized low-density lipoprotein; sd-LDL: small dense low-density lipoprotein

A Malmö study of 6103 individuals, followed up for 10.6 years which investigated the effects of known cardiovascular risk factors on Lp-PLA2, demonstrated that Lp-PLA2 activity and body weight increased with age, particularly in male smokers.[12] In our study, the absence of a difference in smoking rates between groups indicated that smoking would have no effect on study results.

It was shown that Lp-PLA2 inhibition reduced the production of oxidized free fatty acid and lysophosphatidylcholine and it was reported that these products generated by the hydrolysis of ox-LDL through enzymes were mainly responsible for macrophage death in the atheroma plaque, by which mechanism, the direct effect of Lp-PLA2 on atherosclerosis was attempted to be explained.[13]

In the Mayo Heart study, 200 ng/mL was considered as a cardiovascular risk threshold for Lp-PLA2. In the mentioned study, there was a significant correlation between recurrent CVD and Lp-PLA2 activity and as LDL-cholesterol decreased, Lp-PLA2 activity also decreased significantly.[14] In this study, the mean Lp-PLA2 (ng/dL) level was 242.70±49.10 in Group 1, a value which was above the risk threshold mentioned in the Mayo Heart study.

It has been demonstrated that, in the etiopathogenesis of atherosclerosis, paraoxonase 1 enzyme is involved in the antioxidant defense system, since it inhibits lipid peroxidation, slows down or inhibits the development of atherosclerosis by preventing the oxidation of LDL and HDL particles.[15] In this study, the case groups had significantly lower paraoxonase 1 values compared to those in controls. PON1 enzyme, whose protective role in atherosclerosis is well known, tends to decrease in the presence of testosterone deficiency and it is accompanied by high level of Lp-PLA2, which indicates the increased risk of CVD in the presence of testosterone deficiency.

The inflammatory process on the endothelial surface plays an important role in the pathogenesis of atherosclerosis. hs-CRP is used as a cardiovascular risk marker since it predicts the inflammatory process in the early period. In a prospective study by Ballantyne et al.[16] performed on more than 12.000 healthy middle-aged individuals followed up for 6 years to evaluate atherosclerosis (ARIC study), Lp-PLA2 and CRP were found to be independently associated with coronary heart disease.

In this study, no significant difference was noted in the mean hs-CRP values between cases and controls. There was a positive correlation between hs-CRP and several atherosclerotic risk factors such as BMI, waist circumference, body fat percentage, SBP, DBP, and sd-LDL.

A study investigating the anticoagulant effect of testosterone on human showed that hypogonadism was associated with increased incidence of transient ischemic attack, stroke and overall mortality rates and that the infarct area was wider in these patients.[17] In this study, patients with secondary hypogonadism who had the lowest testosterone level had the highest fibrinogen level, though not statistically significant. In addition, fibrinogen was positively correlated with hs-CRP. The secondary hypogonadism group with the highest Lp-PLA2 and the lowest testosterone level, had the highest ox-LDL, hs-CRP, and LDL-cholesterol levels, which indicated that the higher level of Lp-PLA2 in patients with hypogonadism was associated with low testosterone level and even with the extent of low testosterone levels, that most of these effects result from the impact of testosterone on the lipid metabolism and that Lp-PLA2 could be an effective marker for the detection of increased CVD risk due to testosterone deficiency.

The limitation of this study is that the measurement of carotid intima-media thickness, an effective method of detecting atherosclerosis objectively, was not performed.

In conclusion, patients with hypogonadism had significantly higher levels of Lp-PLA2 in this study. Our purpose was to determine whether Lp-PLA2 was involved in the vascular inflammatory process of testosterone deficiency and to elucidate the association between Lp-PLA2 and proatherogenic conditions associated with testosterone deficiency and cardiovascular risk factors. It was considered that CVD risk increased in the presence of testosterone deficiency and Lp-PLA2 could be used as a cardiovascular risk marker for the early detection of this risk. This study, despite the small number of cases, is the first to investigate the association of Lp-PLA2 with testosterone and CVD risk markers in male patients with hypogonadism.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University School of Medicine (11-12/13, 27/12/2011).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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