ORIGINAL

An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males

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Abstract : This clinical study investigated the possible associations of male sex hormone with the extensiveness of coronary artery lesions, coronary heart disease risk factors and ejection fraction of the heart. Ninety six Caucasian male subjects were recruited, 76 with positive and 20 with negative coronary angiograms. Early morning, prior to haemodynamic examination all of them had determined levels of total testosterone, free testosterone, free androgen index (FAI), sex hormone-binding globulin (SHBG), oestradiol, luteinizing hormone, follicle-stimulating hormone, plasma lipids, fibrinogen and glucose. The ejection fraction and the extensiveness of coronary lesions of each subject was assessed on the basis of x-ray examination results using Quantitative Coronary Angiography (QCA) and Left Ventricular Analysis (LVA) packages on the TCS[tm] Acquisition workstation, Medcon.

Men with proven coronary heart disease had significantly lower levels of total testosterone (11.9 vs 21.2 nmol/l), free testosterone (45.53 vs 86.10 pmol/l), free androgen index (36.7 vs 47.3 IU) and oestradiol (109.4 vs 146.4 pmol/l. The level of testosterone was negatively associated with the DUKE Index(1). The most essential negative correlation was observed between SHBG and atherogenic lipid profile (low high-density lipoprotein, high triglycerides). Ejection fraction was substantially lower in patients (51.85 vs 61.30) (without prior myocardial infarction) with low levels of free-testosterone (23.85 vs. 86.10 pmol/l) and FAI (28.4 vs 47.3 IU). A negative correlation was observed between total testosterone, free testosterone, FAI and blood pressure, especially with diastolic pressure.

Men with proven coronary atherosclerosis had lower levels of endogenous androgens than the healthy controls. For the first time in clinical settings it has been demonstrated that low levels of free-testosterone was characteristic for patients with low ejection fraction. Numerous hypothesies for this action can be proposed but all require a proper evaluation process. The main determinant of atherogenic plasma lipid was low levels of SHBG suggesting its main role in developing atheroscerotic lesions. J. Med. Invest. 50 : 162-169, 2003

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INTRODUCTION

In developed countries, coronary artery disease remains a major cause of mortality amongst people over 45 years. It has been confinned that some factors such as cigarette smoking, diabetes mellitus, hyper-

tension, hyperlipideamia promote atherosclerosis. Androgens and especially testosterone are considered responsible for the much higher rate of coronary artery disease in men (2). Several findings appear to support this. The male gender is an independent coronary artery disease risk factor (3, 4). There have been some reports concerning deaths of young body-builders overdosing with synthetic androgens (5). These stereotyped opinions on the role of androgens in cardiology had to be changed according to more recent findings published within the past 5 years.

In rats, castration per se resulted in a significant increase in aortic atherosclerosis (6). An adverse correlation between endogenous testosterone levels and the extensiveness of coronary atherosclerosis has been demonstrated in just one study (7). Some findings indicate that endogenous androgens play a protective role mostly by modulating some risk factors such as lipid profile, hypertension, insulin resistance, fibrinolysis and modulating cytokin levels (8-10).

Previous studies suggested that testosterone may improve symptoms and postexercise ST depression in patients suffering from angina pectoris (11, 12). The vasodilator properties of endogenous male sex hormone have been demonstrated in animal studies (13-15). In humans, testosterone enhances relaxation of the brachial artery (16) and in the coronary artery bed, it produces dilatation and increases blood flow (17, 18). These effects are apparent even with low-doses of testosterone (19).

There are only few laboratory findings suggesting the positive effects of testosterone on left ventricular function. Ejection fraction reduction, diastolic dysfunction develop following gonadodectomy in male rats (20).

In the present study, we investigated the associations between endogenous sex hormone levels and the extensiveness of coronary atherosclerosis, left ventricle ejection fraction and coronary heart disease risk factors.

METHODS

Study design. Included in the study were100 Caucasian men who had had X-ray coronary angiography with left venticulography performed at The Invasive Cardiology Department. Our research was approved by the Local Bioethics Commission.

Before angiographic evaluation blood samples were drawn between 8 a.m. and 10 a.m. All had determined total testosterone, free testosterone, free androgen index (FAI), sex hormone-binding globulin (SHBG), oestradiol, luteinizing hormone, follicle-stimulating hormone, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, partial thromboplastin time, prothrombin time, fibrinogen, glucose. Blood samples were then centrifuged and frozen below -20°C.

The following variables were noted during the examination: age, history of hypertension, diabetes mellitus, cigarettes smoking, behaviour pattern A (interviewed by a psychologist), hyperlipideamia, medications (statin therapy), family history of coronary heart disease, previous myocardial infarction.

Weight, height, systolic and diastolic blood pressures (mean of 5 consecutive measurements) were estimated. The same physician performed all measurements. Body Mass Index was calculated using the formula BMI= weight (kg)/height (m^2).

Participants: 100 men aged 32-72 years, mean 54, were recruited. The inability of proper data collection resulted in the exclusion of 4 men. Elimination criteria were : taking medication influencing sex hormone levels, past history of hypogonadism, thyrotoxicosis, hypothyroidism, restrictive cardiomyopathy, congenitive dyslipidaemia, myocardial infarction within one month before the investigation, homocysteinaemia, pacemaker, previous coronary angioplasty and bypass surgery, valvular heart disease.

Quantative Coronary Angiography module of MDQM Medcon was used to evaluate the extensiveness of coronary lesions. The patients were divided into two groups on the basis of atherosclerosis extensiveness according to the Duke Prognostic CAD Index. It is a prognostic measure related to the anatomic extent and severity of the atherosclerotic involvement of the coronary tree. It was designed to overcome some of the deficiencies of the number of diseased vessels classification. Duke Index is labelling the patient with the worst category applicable upon the estimation of the prognostically important data about lesion severity and its localization. The final index ranges from" 0 to 100."

In the patient group (Group I) 76 patients had at least a 50 percent lesion of at least one vessel (Duke Index>19%).

In the control group (Group II) there were 20 patients without any lesions in the coronary arteries (Duke Index 0). Those patients had positive exercise test results, non-characteristic chest pains and the normal velocity of blood flow within the coronary arteries.

Left ventricle ejection fraction was calculated in ventriculography for every single patient using Left Ventricular Analysis module of MDQM Medcon on

the TCS™ Acquisition workstation, Medcon In the group with lesions were categorized in accordance with the guidance of the American Heart Association Classification of lesion type (21).

Laboratory techniques : All tests were performed at The Local Municipal Hospital.

Serum sex hormone binding globulin (inter-assay coefficient of variation 10.6% and 8.9% at 5.2 nmol/L and 73 nmol/L), sensitivity 0,23 nmol/L, oestradiol (variation of 14.8% at 191 pmol/L and 8.1% at 2830 pmol/L) with a sensitivity of 16 pmol/L, free (with an inter-assay coefficient of variation 5.2% at 15.6 pmol/L and 3.1% at 143 pmol/L), with a sensitivity of 12 pmol/L and total testosterone (inter-assay coefficient of variation 7.8% and 5.6% at 3.3 nmol/L and 16.9 nmol/L, respectively) with sensitivity of 0.23 nmol/L levels were measured by chemiluminescence in enzyme-immuno-assays (Bayer ACS-180, The Chiron Diagnostics ACS : 180 Automated Chemiluminescence Systems).

The enzymatic method was used to assess lipid levels (KoneLab 30, Bio-Merie). All patients had their free androgen index calculated (total testosterone/sex hormone binding globulin (100). Fibrinogen levels were assessed ons a CAM-MTX apparatus (Organon).

Statistical analyses : Values are expressed as mean± 1SD or percentages where appropriate. Pearson's linear correlation coefficient was calculated to test correlations and significance of variables. In the case of a nonlinear value of variables the Spearman correlation test was performed. The Kologorov-Smirnov test was used to evaluate the data distribution. Groups comparison was performed using t test when the data were normally distributed and the Mann-Whitney U nonparametric test when they were not. Chi-square Pearson test for an unpaired model was used to evaluate the statistical correlation of the data shown in Table 1.

Assessment of a statistical correlation between left ejection fraction and sex hormone levels was made after excluding patients with MI (Mann-Whitney U test) (Table 3).

Statistical analyses were performed using the SPSS package, release 8.0.0pl (SPSS. Chicago, IL), with a level of significance of 5%.

RESULTS

Baseline clinical characteristics of the two groups are given in Table 1. Mean age and Body Mass Index were higher in the patient group, however, they were not significantly different. Only cigarette smoking and hypercholesterolaemia as coronary artery disease risk factors were significantly different, whereas other factors (diabetes mellitus, hypertension, age, behaviour pattern A) were not. A past history of myocardial infarction was characterised only in subjects with coronary heart disease.

Table 1. Coronary heart disease risk factors comparison between patients and controls.

	patients (n=76)	controls (n=20)	p
Age [SD](Min-Max)	54.7[18.7](43-72)	48.2[17.4](32-54)	0.086
Behaviour pattern A	28	8	0.7951
BMI [SD](Min-Max)	27.97[14.4](19-35)	26.32[12.5](25-33)	0.513
MI history	36	0	0.0001
Diabetes mellitus	10	2	0.1645
Hypertension	44	16	0.0762
Hipercholesterolaemia	60	8	0.0012
Cig. smoking	55	8	0.0024
Statin therapy	30	8	0.0653

BMI-Body Mass Index
Cig. smoking-Cigarette smoking
MI history-Myocardial infarction history
Max-maximum value
Min-minimum value
p-statistical significance
SD-standard deviation

Seventy-two percent of the men in group 1 were current smokers. Total testosterone and SHBG varied significantly in the current smokers, whereas free-testosterone and FAI did not. In the smokers cohort the means of total testosterone, SHBG and oestradiol were 17.3 nmol/L, 41.9 nmol/L, 118.8 pmol/L, whereas the corresponding means in the non-smokers (11 cases) were 15.5 nmol/L ($p<0.005$), 36.8 nmol/L ($p<0.05$), 111.6 pmol ($p<0.05$).Smokers had significantly higher levels of total testosterone, SGBH and oestradiol.

After adjustment for age and cigarette smoking only the levels of total testosterone, free-testosterone, FAI and oestradiol were significantly lower in the patients group (Table 2).

There were no significant differences in the levels of total cholesterol or LDL between the groups. Subjects with CAD (coronary artery disease) had lower HDL levels, whereas levels of TG were higher.

Subjects from within CAD cohort had higher SBP, DBP, and significantly lower left ventricular ejection fraction (Table 2). After excluding the cases with myocardial infarction and after adjustment for confounders : age, hypertension, cigarette smoking, and the difference in ejection fraction became lower but were still significantly different (cases 51.85 [SD 8.22] vs controls 61.30 [23.37] (Table 3). The same trend was observed with hormone

Table 2. Comparison of laboratory findings between patients and controls.

	Patients n=76 [SD] (Min-Max)	Controls n=20 [SD] (Min-Max)	p
Total testosterone (NR7.5-37.0)nmol/L	11.9[4.8] (2.0-19.9)	21.2[7.4] (15.7-26.8)	<0.012
Free testosterone (NR37.4-138.7pmol/L)	45.53[16.39] (35.00-56.00)	86.10[28.49] (54.00-67.00)	<0.005
Free androgen index (NR18-50IU)	36.7[12.7] (12-47)	47.3[17.8] (21-49)	<0.005
Oestradiol (NR<180pmol/L)	109.4[56.7] (27.0-245.4)	146.4[66.5] (80.4-184.0)	0.003
SHBG (NR15-75nmol/L)	34.35[10.2] (18.00-50.00)	31.35[13.28] (23-40)	0.0575
LH (NR1.3-9.1IU/L)	3.74[1.67] (2.32-5.20)	3.56[1.69] (2.28-4.43)	0.6715
FSH (NR1.7-12.6IU/L)	5.93[1.82] (4.12-28.00)	5.45[0.86] (4.26-6.54)	0.6071
Total cholesterol (NR<5.20mmol/L)	5.66[2.31] (2.56-12.53)	5.31[21.77] (4.53-6.75)	0.8887
LDL (NR<3.36mmol/L)	3.46[1.38] (3.35-6.86)	3.26[1.78] (3.10-3.755)	0.9820
TG (NR<1.8mmol/L)	2.11[0.86] (0.62-4.8)	1.59[0.96] (1.017-3.89)	0.0040
HDL (NR>1.8mmol/L)	1.06[0.47] (0.59-2.20)	1.16[0.48] (1.03-1.29)	0.0117
SBP mmHg	138.25[52.82] (120-210)	133.13[48.55] (110-150)	0.046
DBP mmHg	86.25[31.09] (110-55)	81.09[28.35] (100-80)	0.0179
EF (NR>75%)	49.80[18.44] (33.00-65.00)	61.30[23.37] (56.00-65.00)	<0.005
Fibrinogen (NR200-400mg/L)	386.54[54.77] (240-468.00)	289[44.04] (247-320)	<0.005

DBP-Diastolic blood pressure
EF-ejection fraction
FSH-follicle stimulating hormone
HDL-high-density lipoprotein
LDL-low-density lipoprotein
LH-luteinizing hormone
Max-maximum value
Min-minimum value
NR-normal range
p-statistical significance
SBP-systolic blood pressure
SD-standard deviation
SHBG-sex hormone binding globulin
TG-triglycerides

Table 3. Differences in laboratory findings between patients without MI and controls

	cases=40 [SD] (Min-Max)	controls=20 [SD] (Min-Max)	p
Total testosterone (NR7.5-37.0)nmol/L	12.01[3.4] (6.6-19.9)	21.2[7.4] (15.7-26.8)	<0.012
Free testosterone (NR37.4-138.7pmol/L)	23.85[5] (35-53)	86.10[28.49] (54.00-67.00)	<0.005
Free androgen index (NR18-50IU)	28.4[9.4] (16-44)	47.3[17.8] (21-49)	<0.005
Oestradiol (NR<180pmol/L)	93[38.16] (26.8-202.1)	146.4[66.5] (80.4-184.0)	<0.003
SHBG (NR15-75nmol/L)	33.45[9.75] (18-45)	31.35[11.28] (23-40)	0.0846
LH (NR1.3-9.1IU/L)	3.29[0.91] (2.8-5.2)	3.56[1.69] (2.28-4.43)	0.3426
FSH (NR1.7-12.6IU/L)	5.76[1.43] (4.2-6.49)	5.45[0.86] (4.26-6.54)	0.7898
EF (NR>75%)	51.85[8.22] (35-65)	61.30[23.37] (56.00-65.00)	<0.05

EF-ejection fraction NR-normal range
FSH-follicle stimulating hormone ; LH-luteinizing hormone
Max-maximum value ; Min-minimum value
p-statistical significance ; SD-standard deviation ; SHBG-sex hormone binding globulin

levels, which were slightly lower in cases without MI compared with controls.

In haematological examination, only fibrinogen was essentially higher in CAD patients (Table 2).

In both groups FAI and free-testosterone were negatively associated with HDL, while SHBG and oestradiol were positively associated with HDL (Table 4). FAI and free-testosterone were positively associated with triglycerides, while SHBG negatively. FAI and free-testosterone negatively associated with SBP, DBP and fibrinogen. Free testosterone levels were negatively associated with the degree in the Duke Index whereas none of the hormones correlated with lesion type (Spearman correlation coefficient) (data not shown).

DISCUSSION

In the present study, men with coronary heart disease were found to have significantly lower levels of endogenous sex hormones than males without any atherosclerotic lesions in the coronary bed.

Two groups of patients were investigated. Group 1 consisted of men with lesions documented in angiograms, with a Duke Index greater than 19%. Patients with no evidence of atherosclerotic lesions were included in group 2. Not surprisingly these groups differed from each other significantly by several coronary risk factors (see Table 1). However, after adjustment for confounders, endogenous sex hormone levels remained essentially lower in men with proven coronary heart disease (table 2). Moreover, free testosterone levels were negatively correlated with the extensiveness of atherosclerosis in the coronary bed (5). Several prior studies investigating the possibilities of such associations have reported conflicting

results. English et al. did not find any correlation between sex hormone levels and the intensity of atherosclerotic lesion (7). A different method used in assessing the extensiveness of atherosclerosis may have caused this inconsistency in the results. The present study was an observational one and experimental and clinical human studies are clearly needed to verify the validity of these present findings. Future investigations should include a much larger group of patients. A major action of statins is to inhibit the synthesis of cholesterol in different cells. Theoretically, lowering the cholesterol levels can disrupt the steroid hormone synthesis. Such an affect was not demonstrated in numerous clinical trials. In the 4S examination, the rate of male impotency was similar in the groups receiving statin treatment and placebo.

Statin therapy was more frequently used by coronary heart patients but simultaneously total cholesterol levels were higher than in the control group. Based on this, the assumption that statin therapy decreases endogenous testosterone precursor levels is groundless. In addition, in clinical studies it has been shown that such treatment did not affect steroidogenesis and therefore does not influence testosterone levels (22). Androgens in general are widely suggested to have positive effects on atherogenic lipid profile by reducing the levels of total cholesterol, LDL, VLDL and apolipoprotein A1 (8, 23, 24). In the present study SHBG and endogenous sex hormone levels were significantly correlated with HDL and TG, respectively, but not with LDL and total cholesterol levels. Unfortunately VLDL levels were not considered because only 50% of the cases had been measured.

SHBG correlated positively with HDL levels, and negatively with TG levels (Table 4). Similar associations were found with total testosterone but they did not reach statistical significance. The opposite correlations were observed in the case of free testosterone and FAI, which correlated negatively with HDL and positively with TG levels (Table 4). Most clinical studies assess the influence of total, free testosterone on plasma lipids underestimating the role of SHBG. Only in three studies (25-27) have decreased levels of HDL and SHBG after exogenous testosterone supplementation been reported. Pugeat *et al*. suggested that SHBG increase HDL levels through an effect on hepatic lipoprotein lipase biosynthesis (27). As suggested by Gyllenborg et al., another possible mechanism for SHBG influencing HDL metabolism is by some unidentified receptor. In the present investigation, atherogenic lipid profile was associated with low levels of SHBG and high levels of free testosterone. However FAI and free testosterone levels were significantly negatively associated with fibrinogen levels (Table 4). This observation parallels findings from previous studies. Bioavailable testosterone positively modifies coronary heart disease risk profile by its direct effect on endothelium

Table 4. Correlations between sex hormone levels and variables

cases=Rp[p] controls=Rp[p]	Total testosterone	Free androgen index	Free-testosterone	SHBG	Oestradiol
HDL	-0.43[0.66] (-0.6[0.34])	-0.85[0.042] (-0.89[0.031])	-0.89[0.033] (-0.91[0.005])	0.86[0.034] (0.93[0.002])	0.79[0.026] (0.76[0.037])
TG	0.322[0.451] (0.367[0.393])	0.78[0.053] (0.82[0.047])	0.81[0.048] (0.94[0.039])	-0.87[0.021] (-0.94[0.018])	-0.56[0.354] (-0.64[0.673])
EF*	0.73[0.049] (0.78[0.043])	0.76[0.042] (0.84[0.004])	0.95[0.002] (0.86[0.043])	-0.65[0.202] (0.74[0.639])	0.45[0.632] (0.84[0.432])
SBP	-0.5[0.328] (-0.34[0.431])	-0.79[0.047] (-0.89[0.009])	-0.87[0.037] (-0.82[0.048])	0.32[0.771] (0.54[0.07])	-0.76[0.056] -0.89[0.049])
DBP	-0.67[0.278] (-0.78[0.087])	-0.89[0.046] (-0.94[0.038])	-0.93[0.034] (-0.87[0.005])	0.56[0.783] 0.76[0.076])	0.62[0.092] 0.46[0.539])
Fibrinogen	-0.74[0.173] (-0.67[0.429])	-0.76[0.045] (-0.78[0.028])	-0.85[0.029] (-0.94[0.003])	0.32[0.202] (0.56[0.492])	0.59[0.482] (0.76[0.083])
Duke Index	-0.07[0.5]	-0.79[0.061]	-0. -69[0.048]	-0.17[0.140]	-0.67[0.05]

*cases n=40
EF-ejection fraction
DBP-diastolic blood pressure
HDL-high-density lipoprotein
p-statistical significance
SBP-systolic blood pressure
SHBG-sex hormone binding globulin ; TG-triglycerides

and fibrinolysis (18, 29). Thus, it can be suggested that endogenous sex hormone levels slow lesion progression by influencing other, than plasma lipid, risk factors. All this should be confirmed in well designed, double-blind studies. Further investigations are necessary (30).

SHBG is a glycoprotein synthesised by hepar that specifically binds approximately 60% of testosterone, almost all 5α-dihydrotestosterone (DHT) and less then 40% of 17 β-oestradiol. Transporting sex hormones in the blood vessels is not the sole function of SHBG. It is responsible for the proper recognition of the destination cells and for the weakening of the biologic activity of sex hormones. The high level of testosterone inhibits the synthesis of SHBG, while oestradiol and thyroid hormones act oppositely.

Levels of SHBG and oestradiol increase, whereas levels of total and free testosterone decrease with age. SHBG levels are higher in women than in men of corresponding age. These differences diminish over 65 years old (31). Taking all this into consideration the conclusion can be drawn that plasma lipid profile is affected in a positive way by a rise in SHBG levels and negatively by an increase in free testosterone levels.

In the present study, a significant difference was noted in the ejection fraction measurements between the two groups. A comparison of cohorts was performed after the exclusion of patients with MI. In the analyses after adjustment for confounders (age, cigarette smoking, and hypertension) the levels of total free testosterone and oestradiol remained lower in coronary heart disease patients (Table 3). There is no consensus on the effect of endogenous sex hormones on ejection fraction. There is no clinical trial findings concerning the effects of testosterone on the left ventricular function. In rats, testosterone, when administered intramuscularly increases peak myocardial oxygen consumption and attenuates sarcomers shortening thus improving the heart function (20). Castration results in reduced ejection fraction and diastolic dysfunction of the left ventricle. LeGross et al. found that testosterone analogues taken orally cause diastolic dysfunction of the heart (32). Clinical trials are needed to evaluate the effects of androgen on the contractility of the heart.

In the present investigation endogenous sex hormone levels negatively correlated with the extensiveness of coronary atherosclerosis. This effect was multi-dimensional and its aspects are not fully investigated. Previous findings lack an unambiguous opinion on the role of male sex hormones on the development of the coronary atherosclerotic lesions. In the present investigation endogenous sex hormones modified several coronary heart disease risk factors. SHBG levels negatively correlated with atherogenic plasma lipid profile. Free testosterone levels correlated positively with both, low fibrinogen levels and high ejection fraction of the heart. Patients with higher levels of endogenous sex hormones had significantly lower blood pressures, with the strongest positive correlation between free testosterone levels and diastolic blood pressure.

In conclusion, the results of the present investigation suggest that :

1) SHBG may play a dominant role in influencing the progression of lesions via the plasma lipid profile;
2) higher levels of free testosterone and FAI improve the ejection fraction ;
3) higher levels of male sex hormones were associated with patients with no atherosclerotic lesions ;
4) androgen replacement therapy can be useful in certain male patients, especially elderly.

For some time, a renewal of interest in sex hormones as cardioactive substances can be observed in the world literature. The results of various studies are slowly changing the views of male sex hormones as a major coronary risk factor.

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