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ORIGINAL ARTICLE

Total testosterone levels, metabolic parameters, cardiac remodeling and exercise capacity in coronary artery disease patients with different stages of glucose tolerance

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Objective and methods. **The correlation between total testosterone levels, exercise capacity, and metabolic and echocardiographic parameters was studied in 1097 male subjects with coronary artery disease (CAD) and different stages of glucose tolerance.**

Results. **Testosterone level was the lowest among diabetics as compared to prediabetics or controls ($P < 0.001$). Total and abdominal adiposity were the highest in the subjects with the lowest testosterone. Independent of adiposity, fasting glucose, insulin, and leptin were higher ($P < 0.03$ to < 0.001) among diabetic and control groups in the lowest, and HbA1c values ($P < 0.001$) higher among diabetics in the lowest, than in the highest testosterone tertile. Controls and prediabetic subjects with the lowest testosterone levels had the lowest HDL-cholesterol levels, and controls also the highest triglycerides. An association between low testosterone level and low maximal exercise capacity was observed in diabetics ($P < 0.001$) and controls ($P < 0.03$). Independent of adiposity and metabolic parameters, low testosterone levels were associated with the highest septal wall thickness ($P < 0.03$) among diabetics.**

Conclusion. **A negative correlation between low testosterone and dysmetabolic features was observed. Independent of metabolic status, low plasma testosterone seems to be an indicator of impaired maximal exercise capacity and cardiac hypertrophy among CAD patients with type II diabetes.**

key words: Body mass index, cardiac echo, diabetes, testosterone

Key messages

- A clear correlation between low total testosterone and deleterious metabolic profile was shown in both groups of normal and impaired glucose tolerance.
- Maximal exercise capacity is the lowest among patients with the lowest testosterone levels.
- Plasma testosterone seemed to be an independent indicator of septal wall thickness among diabetics.

Introduction

Male gender is a strong cardiovascular risk factor. The reason behind this is not completely understood, but hormonal factors may be involved. Low testosterone has been shown to cause increased mortality in men (1–3). Metabolic syndrome and type 2 diabetes are associated with strongly increased cardiovascular risk. Low testosterone is associated with insulin resistance, hyperglycemia, hypertension, dyslipidemia, and visceral obesity, all key factors of the metabolic syndrome and type 2 diabetes (4–7). Epidemiological studies have reported that low testosterone levels are an independent risk factor for type 2 diabetes (8–10). It has been shown that men with Klinefelter's syndrome (a classical cause of hypogonadism) have an increased incidence of diabetes (11). In this study we wanted to investigate more about the correlation between testosterone deficiency and glucose and insulin metabolism, especially the role of testosterone in subjects with normal glucose tolerance and prediabetes.

In the present study we concentrate on the relation between low testosterone and cardiometabolic risk in males. The role of testosterone in cardiovascular disease is not yet completely explained. Low testosterone levels have been associated with conventional cardiovascular risk factors and increased expression of mediators of the atherosclerotic process (12). Another factor that has been proposed is the possible effect of testosterone on cardiac remodeling (13,14), such as left ventricular hypertrophy, and systolic and diastolic function, which are all associated with increased cardiovascular morbidity and mortality in various populations (15–17). For example, left ventricular hypertrophy (LVH) in young men may be related to indices of enhanced sympathetic nervous system reactivity and with elevated fasting insulin and triglyceride levels, which may be caused by insulin resistance (18). Blood pressure and body mass are the most important risk

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factors for increased LV mass, and both tend to increase with age (19), while testosterone levels decrease with aging (13). A significant amount, in some studies nearly half (20), of the ventricular mass variability remains unexplained. Whether the differences in left ventricular mass are related to endogenous sex hormone concentrations has not been completely clarified. In this study we wanted to investigate the role of total fasting testosterone in left ventricular mass and other echocardiographic parameters as well as maximal exercise capacity during exercise test in subjects with normal glucose tolerance, those with prediabetes, and those with manifest type 2 diabetes.

Materials and methods

Clinical methods

The study population consisted of 489 male patients with coronary artery disease (CAD) and type 2 diabetes and 608 patients with CAD but without manifest diabetes from the Cardiovascular Complications in Type II diabetes (ARTEMIS) study. The ARTEMIS study is registered at ClinicalTrials.gov, Record 1539/31/06. The patients for this study are recruited from the consecutive series of patients undergoing coronary angiography in the division of cardiology of the Oulu University Hospital. The diabetes and non-diabetes groups are matched in terms of following variables: 1) sex, 2) age, 3) history of myocardial infarction (1:1), and 4) type of coronary intervention after angiography (1:1 revascularization, coronary artery bypass, or coronary angioplasty). Screening was executed from the register of the coronary angiography patients of the University Hospital of Oulu, if the coronary angiography had been performed within 1 year before entering the study. Patients with angiographically documented coronary artery disease were included in the study. Exclusion criteria were: NYHA class IV despite appropriate treatment of heart failure; pacemakers or planned pacemaker implantation; participation in a competing clinical trial that is not accepted by the Steering Committee; psychologically or physically (due to any other illness) unfit for participation in the study according to the opinion of the investigator; patient compliance doubtful; patients who are geographically or otherwise inaccessible for follow-up; pregnancy; life expectancy <1 year; end-stage renal failure needing dialysis or creatinine >250 μmol/L; and age <18 years.

After fulfilling the inclusion and exclusion criteria, the patients underwent extensive risk profiling at the baseline. Before inclusion in the study, the patients without diabetes underwent a 2-hour oral glucose tolerance test (OGTT) to exclude diabetes and/or abnormal glucose tolerance. Diabetes was defined as fasting capillary plasma glucose levels ≥ 7.0 and/or a 2-hour post-load value in the OGTT ≥ 12.2 mmol/L according to the definition and diagnosis of diabetes mellitus and intermediate hyperglycemia (21). Patients with normal glucose tolerance must be normoglycemic, defined as plasma capillary glucose levels <6.1 mmol/L in the fasting state and a 2-hour post-load value <8.9 mmol/L in the OGTT. Impaired glucose tolerance (IGT) was defined as fasting capillary plasma glucose <7.0 mmol/L and 2-hour glucose ≥ 8.9 but <12.1 mmol/L. Finally, in impaired fasting glucose (IFG) fasting plasma capillary glucose should be between 6.1 and 6.9 mmol/L, and 2-hour glucose <8.9 mmol/L.

Body weight was measured with a digital scale. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured to the nearest 0.5 cm with a tape measure midway between the lower rib margin and the iliac crest in light expirium. Blood pressure was measured in a sitting position from the right arm with an oscillometric device (Dinamap® model 18465X; Criticon Ltd, Ascot, UK) after an overnight fast and after a rest.

Maximal exercise capacity during exercise test was measured. The patients performed an incremental maximal test on a bicycle ergometer (Monark Ergomedic 839 E; Monark Exercise AB, Vansbro, Sweden), starting at 30 W with the work rate increasing at a rate of 15 W every 1 min until exhaustion. The patients moved to the supine position within 30 s after cessation of exercise. The patients were not allowed to move or talk during the recovery phase. Ventilation (V_E) and gas exchange (M909 Ergospirometer; Medikro, Kuopio, Finland) were measured and reported as the mean value for every minute. The highest 1-min mean value of oxygen consumption was expressed as the peak oxygen consumption (VO_{2peak}). Maximal workload (W) and maximal metabolic equivalents (METs) were calculated as average workload and METs during the last 1 min of the test.

Laboratory measurements

All measurements were done, and venous blood samples into EDTA tubes were obtained after a 12-hour overnight fast by using standardized methods.

After fasting blood samples had been drawn, the subjects without known diabetes were given a 75-g glucose load. Both 1-hour and 2-hour capillary glucose were determined, except from those with previously known diabetics. Capillary (plasma referenced) glucose was analyzed by glucose oxidase method with the OneTouch® UltraEasy® Test Strips with FastDraw™ (LifeScan, Switzerland). Serum insulin, glycated hemoglobin (HbA1c), and lipids were analyzed by hospital laboratory. Fasting serum insulin levels were measured by two-site sandwich immunoassay using direct chemiluminescent technology (Advia Centaur Insulin; Siemens Healthcare Diagnostics, Tarrytown, NY 10591-5097 USA; total coefficient of variations (CVs) 4%–7% and intra-assay precisions of 4%–5%).

HbA1c was analyzed by Latex immunoturbidimetric assay (Advia Chemistry Systems, Siemens Healthcare Diagnostics). Considering lipoproteins, high-density lipoprotein (HDL) cholesterol was analyzed by enzymatic, direct kinetic assay (Direct HDL Cholesterol (D-HDL); Siemens Healthcare Diagnostics), low-density lipoprotein (LDL) by elimination/catalase assay (Direct LDL Cholesterol (DLDL); Siemens Healthcare Diagnostics), and triglycerides by enzymatic-G3PO-Endpoint assay (Siemens Healthcare Diagnostics).

Leptin levels were measured by MilliPlex map Human Metabolic Hormone Panel kit (Millipore Corporation, Billerica, MA, USA) (cat no HMH-34K; precision, %: intra-assay <9, inter-assay <8). Fasting total testosterone levels were analyzed by the liquid chromatography tandem mass spectrometry method (22).

Two-dimensional, m-mode and Doppler echocardiography was performed according to the American Society of Echocardiography (ASE) guidelines by three cardiologists (O.-P.P., S.L., J.N.) utilizing General Electric Vivid 7 (Providian Medical Equipment LLC. 30510 Lakeland Blvd., Unit A, Willowick, Ohio, 44095) ultrasound machine. The echocardiographic parameters chosen for further study were LV ejection fraction (EF), left ventricular mass index (LVMI), E/E', E/A, isovolumic relaxation time (IVRT), and septal wall thickness. EF reflects the systolic function of left ventricle, whereas E/E', E/A, measured from tissue Doppler recordings of the septal wall, and IVRT reflect left ventricular diastolic function. Left ventricular mass was calculated using the formula recommended by the ASE ($\text{LV mass} = 0.8 \times (1.04\ ((\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3)) + 0.6$ g). Left ventricular mass index (LVMI) was calculated by dividing LV mass with body surface area (BSA).

Table I. Medications of the patients by testosterone tertiles.

	Diabetics			Prediabetics			Controls		
Study group	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
Testosterone tertile									
Age (years)	66.3 (0.7)	65.8 (0.7)	66.4 (0.7)	66.3 (0.9)	68.6 (0.9)	67.5 (0.9)	66.0 (0.8)	64.8 (0.8)	65.2 (0.8)
Current smokers, %	12	13	7	8	4	6	6	14	15
History of AMI	44	50	42	61	50	47	47	48	48
Medication									
Antithrombotics	95	99	98	97	96	97	99	98	99
Beta-blockers	92	89	92	94	90	82	90	81	85
Calcium-channel blockers	42*	35	23	21	25	15	16	16	13
ACEI	47	50	43	53	38	39	44	35	39
AT2	24	27	22	24	15	18	13	25**	13
Diuretics	53*	47	31	29	13**	22	21	25	13
Lipid-lowering medication	90	93	93	94	93	93	91	92	91
Diet only for diabetes	12	15	22	–	–	–	–	–	–
Oral antidiabetic medication	53	57	56	–	–	–	–	–	–
Insulin	10	9	7	–	–	–	–	–	–
Insulin + oral antidiabetic medication	25	19	15	–	–	–	–	–	–
Nitrates	51	37**	41	25	40	26	37	21**	28

Values are mean (SE) or percentages.
*$P < 0.01$; **$P < 0.05$.
ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; AT2 = angiotensin II receptor blocker; BMI = body mass index.

Statistical analyses

SPSS (version 18.0; SPSS, Inc., Chicago, IL, USA) statistical package was used in all statistical analyses. Analyses of mean values were performed using one-way analysis of variance (ANOVA) and one-way analysis of covariance (ANCOVA) with Bonferroni-correction for multiple and pairwise comparisons. For ANOVA and ANCOVA analyses the subjects were divided into tertiles of total testosterone levels. Log-transformed values were used as appropriate to normalize the skewed distributions whenever needed (leptin, insulin, HbA1c, triglycerides, and E/A). $P < 0.05$ was regarded as statistically significant. Correlations were tested with Pearson's correlation.

Results

A total of 1097 men were taken into this study. In the whole study population, plasma testosterone concentration correlated significantly with BMI ($R = -0.328$, $P < 0.001$), waist circumference ($R = -0.371$, $P < 0.001$), HbA1c ($R = -0.279$, $P < 0.001$), fasting ($R = -0.266$, $P < 0.001$) and 2-hour glucose ($R = -0.152$, $P < 0.001$) during OGTT; plasma HDL-cholesterol ($R = 0.248$ $P < 0.001$), triglycerides ($R = -0.196$, $P < 0.001$), E/E' ($R = -0.127$, $P < 0.001$), septal wall thickness ($R = -0.157$, $P < 0.001$), and maximal watts ($R = 0.160$, $P < 0.001$) or METs ($R = 0.308$, $P < 0.001$) during exercise test.

The men were divided into three groups, the first group being the ones with diagnosed type 2 diabetes ($n = 489$), the second group the control subjects ($n = 392$), and the third croup consisting of the prediabetic (IFG + IGT) subjects ($n = 216$). Total testosterone level was lower (11.6 nmol/l (SD 5.0)) among diabetics than among prediabetic (14.2 nmol/l (SD 5.6)) or control subjects (15.1 nmol/l (SD 5.3)) ($P < 0.001$) before and after adjustment for age, BMI, and waist circumference. Because of marked differences in testosterone levels between diabetic and non-diabetic groups we decided to analyze the results on testosterone in different glucose tolerance groups. In further analyses, all groups were divided into three subgroups according to tertiles of total testosterone.

General characteristics and use of selected medications in study groups by testosterone tertile are given in Table I. The use of calcium-channel blockers and diuretics was higher among diabetics with the lowest than in the highest testosterone levels. The frequency of use of angiotensin-converting enzyme inhibitors among controls, diuretics among prediabetics, and nitrates among diabetics and controls showed differences between

Table II. Characteristics of the diabetic subjects ($n = 489$) according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd			
n	165		161		163		P [a]	P [b]
Age (years)	66.3	(0.7)	65.8	(0.7)	66.4	(0.7)	NS	
Testosterone (nmol/L)	7.2	(0.2)	10.5	(0.2)	17.3	(0.2)	<0.001	
BMI (kg/m^2)	31.4	(0.4)	29.8	(0.4)	28.4	(0.4)	<0.001	<0.001[c,d,e]
Waist (cm)	110.7	(0.9)	106.2	(1.0)	101.8	(1.0)	<0.001	<0.03[c]
Leptin (ng/mL)	2.5	(0.1)	1.6	(0.1)	1.4	(0.1)	<0.001	<0.001[c,d]
Systolic BP (mmHg)	144.8	(1.8)	143.7	(1.8)	146.2	(1.8)	NS	NS
Diastolic BP (mmHg)	80.8	(0.9)	81.3	(0.9)	82.1	(0.9)	NS	NS
HbA1c (%)	7.4	(0.1)	7.0	(0.1)	6.8	(0.1)	<0.001	<0.01[c,d]
Fasting glucose (mmol/L)	8.1	(0.2)	7.4	(0.2)	7.2	(0.2)	<0.01	<0.03[c,d]
Fasting insulin (mU/L)	30.9	(6.6)	35.8	(6.6)	19.9	(6.6)	<0.001	<0.03[c]
Total cholesterol (mmol/L)	3.8	(0.1)	3.7	(0.1)	3.9	(0.1)	NS	NS
HDL-cholesterol (mmol/L)	1.12	(0.02)	1.12	(0.02)	1.19	(0.02)	<0.03	NS
Triglycerides (mmol/L)	1.8	(0.1)	1.6	(0.1)	1.5	(0.1)	<0.01	NS

[a]*P* values obtained from ANCOVA analyses before adjustment for age and BMI (except for BMI).
[b]*P* values obtained from ANCOVA analyses after adjustment for age and BMI (except for BMI).
[c–e] In *post-hoc* analyses significance between tertiles 1 and 3 ([c]), 1 and 2 ([d]), or 2 and 3 ([e]).

Table III. Characteristics of the control subjects ($n = 392$) according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd			
n	133		129		130		P [a]	P [b]
Age (years)	66.0	(0.8)	64.8	(0.8)	65.2	(0.8)	NS	
Testosterone (nmol/L)	9.7	(0.2)	14.3	(0.2)	21.2	(0.2)	<0.001	
BMI (kg/m^2)	27.4	(0.3)	26.9	(0.3)	25.7	(0.3)	<0.001	$<0.001^{c}$
Waist (cm)	99.2	(0.8)	97.2	(0.8)	93.6	(0.8)	<0.001	$<0.01^{c}$
Leptin (ng/mL)	1.3	(0.2)	1.2	(0.2)	0.8	(0.2)	<0.001	$<0.03^{c}$
Systolic BP (mmHg)	142.8	(2.0)	145.8	(2.1)	143.2	(2.1)	NS	NS
Diastolic BP (mmHg)	80.9	(0.9)	82.0	(0.9)	80.9	(0.9)	NS	NS
HbA1c (%)	5.83	(0.03)	5.83	(0.03)	5.77	(0.03)	NS	NS
Fasting glucose (mmol/L)	5.54	(0.04)	5.35	(0.04)	5.32	(0.04)	<0.001	$<0.001^{c,d}$
Fasting insulin (mU/L)	11.9	(0.5)	9.9	(0.5)	8.9	(0.5)	<0.001	$<0.01^{c,d}$
Total cholesterol (mmol/L)	3.8	(0.1)	3.9	(0.1)	4.1	(0.1)	NS	NS
HDL-cholesterol (mmol/L)	1.16	(0.02)	1.28	(0.02)	1.33	(0.02)	<0.001	$<0.001^{c,d}$
Triglycerides (mmol/L)	1.30	(0.05)	1.12	(0.05)	1.07	(0.05)	<0.01	$<0.03^{c,d}$

[a]*P* values obtained from ANCOVA analyses before adjustment for age and BMI (except for BMI).
[b]*P* values obtained from ANCOVA analyses after adjustment for age and BMI (except for BMI).
[c,d]In *post-hoc* analyses significance between tertiles 1 and 3 ([c]), or 1 and 2 ([d]).

testosterone groups, with patients belonging to the medium tertile showing different frequency.

In Table II the characteristics of the diabetic subjects by testosterone tertiles are shown. BMI, waist circumference, plasma leptin, HbA1c, fasting glucose, insulin, HDL-cholesterol, and plasma triglyceride levels differed significantly between testosterone tertiles before adjustments. The association between waist, leptin, HbA1c, fasting glucose, and insulin levels and testosterone tertile persisted after adjustment for age and BMI. The patients belonging to the lowest testosterone tertile showed the highest BMI, waist, leptin, HbA1c, glucose, and insulin levels compared to those in the highest tertile. The differences in BMI, leptin, HbA1c, and fasting glucose levels were also significant between testosterone tertiles 1 and 2. BMI was also higher in tertile 2 versus 3.

Table III shows the anthropometric and metabolic characteristics in the control subjects according to testosterone tertiles. BMI, waist circumference, fasting glucose, insulin, leptin, and triglycerides were higher and HDL-cholesterol lower in the lowest than in the highest testosterone tertile after adjustment for age and total fatness (except for BMI). The differences in fasting glucose and insulin were also significant between tertiles 1 and 2.

In Table IV the same parameters as in Tables II and III in testosterone tertiles are shown in prediabetic subjects. The association of testosterone with waist ($P<0.01$) and HDL-cholesterol ($P<0.03$) persisted after adjustment for age and BMI.

Tables V–VII show the echo parameters and maximal exercise capacity during exercise test according to testosterone tertiles in different glucose tolerance groups. Among the diabetic group (Table V) LVMI ($P<0.05$) and septal wall thickness ($P<0.03$) adjusted for age, BMI (except LVMI), systolic blood pressure, and heart rate were higher in the lowest than in the highest testosterone tertile. Further adjustment for metabolic parameters (triglycerides, insulin, or HbA1c) changed the association between LVMI and testosterone tertile to a non-significant level. However, the association with septal wall thickness persisted after these metabolic parameters or medications were taken into account. Septal wall thickness ($P<0.03$) and E/E' ($P<0.01$) were also higher in the lowest than in the medium testosterone tertile group. Furthermore, maximal exercise capacity expressed as maximal watts or METs ($P<0.001$ for both) during exercise test adjusted for age and BMI were lower in the patients who belonged to the lowest than to the highest testosterone tertile. METs during exercise test differed also significantly between the medium and highest tertiles. Further adjustment of maximal exercise capacity for EF, smoking, metabolic parameters, or physical activity level during leisure time or work did not change these associations to a non-significant level (Table V).

Among control patients E/A varied significantly according to testosterone levels in such a manner that the medium tertile was associated with the lowest value ($P<0.03$) (Table VI).

Table IV. Characteristics of the prediabetic subjects ($n = 216$) according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd			
n	72		72		72		P [a]	P [b]
Age (years)	66.3	(0.9)	68.9	(0.9)	67.5	(0.9)	NS	
Testosterone (nmol/L)	8.8	(0.3)	13.3	(0.3)	20.6	(0.3)	<0.001	
BMI (kg/m^2)	28.4	(0.4)	26.5	(0.4)	27.0	(0.4)	<0.01	$<0.03^{d}$
Waist (cm)	103.5	(1.2)	97.6	(1.2)	97.0	(1.2)	<0.001	$<0.01^{c}$
Leptin (ng/mL)	1.7	(0.2)	1.0	(0.2)	1.3	(0.2)	<0.05	NS
Systolic BP (mmHg)	144.9	(2.7)	144.8	(2.7)	150.3	(2.7)	NS	NS
Diastolic BP (mmHg)	81.0	(1.4)	79.7	(1.4)	82.5	(1.4)	NS	NS
HbA1c (%)	6.02	(0.06)	5.86	(0.06)	5.91	(0.06)	NS	NS
Fasting glucose (mmol/L)	6.02	(0.07)	6.02	(0.07)	6.03	(0.07)	NS	NS
Fasting insulin (mU/L)	14.2	(0.8)	10.9	(0.8)	12.4	(0.8)	<0.03	NS
Total cholesterol (mmol/L)	3.8	(0.1)	3.9	(0.1)	4.0	(0.1)	NS	NS
HDL-cholesterol (mmol/L)	1.16	(0.03)	1.20	(0.03)	1.29	(0.03)	<0.05	$<0.03^{c}$
Triglycerides (mmol/L)	1.39	(0.08)	1.23	(0.08)	1.20	(0.08)	NS	NS

[a]*P* values obtained from ANCOVA analyses before adjustment for age and BMI (except for BMI).
[b]*P* values obtained from ANCOVA analyses after adjustment for age and BMI (except for BMI).
[c,d]In *post-hoc* analyses significance between tertiles 1 and 3 ([c]), or 1 and 2 ([d]).

Table V. Echo parameters and maximal exercise capacity during exercise test in the diabetic subjects according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd		P^a	P^b
LVMI (g/m^2)	115.4	(2.2)	110.3	(2.2)	108.6	(2.2)	$<0.05^c$	–
EF (%)	61.9	(0.8)	63.2	(0.8)	63.3	(0.8)	NS	NS
E/E'	11.7	(4.4)	10.3	(3.3)	10.8	(3.8)	<0.01	$<0.01^d$
E/A	1.08	(0.04)	1.02	(0.04)	1.10	(0.03)	NS	NS
IVRT (ms)	102.1	(2.0)	96.8	(2.0)	101.5	(2.0)	NS	NS
Septal wall (mm)	12.4	(0.17)	11.6	(0.17)	11.5	(0.17)	<0.001	$<0.03^{c,d}$
Max watts during exercise test	119.7	(2.9)	128.7	(2.9)	135.0	(2.9)	<0.001	$<0.001^c$
Max METs during exercise test	4.6	(0.1)	5.1	(0.1)	5.6	(0.1)	<0.001	$<0.001^{c,e}$

[a,b]*P* values obtained from ANCOVA analyses adjusted for age, systolic blood pressure, and heart rate ([a]) or age, systolic blood pressure, heart rate, and BMI ([b]). LVMI was not adjusted for BMI. Maximal exercise capacity adjusted for age ([a]) or age and BMI ([b]).
[c–e]In *post-hoc* analyses significance between tertiles 1 and 3 ([c]), 1 and 2 ([d]), or 2 and 3 ([e]).
EF = LV ejection fraction; IVRT = isovolumic relaxation time; LVMI = left ventricular mass index; MET = metabolic equivalent.

In addition, the subjects belonging to the lowest testosterone tertile had the lowest maximal METs during exercise test after adjustment for age and BMI ($P < 0.03$) (Table VI).

Echo parameters or maximal exercise capacity during the exercise test in the prediabetic subjects were not different between the testosterone tertiles (Table VII).

Discussion

In this study we found a clear correlation between low total testosterone and total and abdominal adiposity. Low testosterone was also associated independently with several metabolic aberrations, such as worsened glucose control, increased insulin resistance, low HDL-cholesterol, and high triglyceride levels. Low plasma testosterone seems also to be an indicator of impaired maximal exercise capacity and cardiac hypertrophy indexes, particularly among coronary artery disease patients with type 2 diabetes independent of metabolic parameters. The reason for the lowest E/E' in subjects with medium testosterone tertile is difficult to explain.

Low testosterone has been associated with obesity in several earlier studies (23,24) including the present one. The total testosterone was clearly inversely correlated with BMI and waist circumference in all our glucose tolerance subgroups. Obesity has also been suggested to be the driving factor for testosterone deficiency. With increasing adiposity, there is an increase of aromatase activity that is associated with further depression of testosterone concentrations leading to the increased preferential deposition of abdominal fat. The latter phenomenon, in turn, leads to a progressive hypogonadal state (25). Low testosterone can also be a driving factor for obesity. Lipoprotein lipase and leptin are two key proteins in adipose tissues that are regulated by sex steroid hormones (26). The relationship between low testosterone and abdominal obesity is partly caused by increased lipoprotein lipase activity, increased triglyceride uptake, and decreased lipolysis (27). A close association between serum levels of testosterone and leptin in males has been earlier observed (28). In our data high leptin levels were independently associated with low testosterone among diabetic and control subjects. Since subjects with low testosterone were more obese, they most probably have leptin resistance.

Low levels of total testosterone are associated with increased risk of developing metabolic syndrome over time in non-obese men (10). Testosterone therapy has been shown to reduce waist circumference and body fat mass in hypogonadal men (29–32). Our cross-sectional study shows an inverse correlation between fasting glucose and total testosterone in subjects with normal glucose tolerance. This supports the previous findings that low testosterone in men is a risk factor for type 2 diabetes (8–10,33). The finding that in prediabetic patients there seemed not to exist any correlation between testosterone and glucose parameters was somewhat controversial. However, this could be due to a prevalence issue since the number of prediabetic subjects was clearly smaller than that in the other groups.

In the diabetic subgroup low testosterone was associated with worsened glucose control. Testosterone therapy has been shown to improve metabolic control in hypogonadal men with and without type 2 diabetes (30,32,34–36). Increase of left ventricular mass is associated with obesity (19). Other factors associated with left ventricular hypertrophy include enhanced sympathetic nervous

Table VI. Echo parameters and maximal exercise capacity during exercise test in the control subjects according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd		P^a	P^b
LVMI (g/m^2)	110.6	(2.3)	108.9	(2.3)	110.6	(2.3)	NS	
EF (%)	64.4	(0.7)	63.9	(0.7)	62.8	(0.7)	NS	NS
E/E'	9.9	(0.3)	9.8	(0.3)	9.3	(0.3)	NS	NS
E/A	1.18	(0.04)	1.11	(0.04)	1.17	(0.04)	<0.03	<0.03
IVRT (ms)	103.6	(1.9)	103.8	(1.9)	101.5	(1.9)	NS	NS
Septal wall (cm)	1.12	(0.02)	1.10	(0.02)	1.08	(0.02)	NS	NS
Max watts during exercise test	141.8	(3.3)	152.3	(3.4)	147.6	(3.4)	NS	NS
Max METs during exercise test	6.0	(0.1)	6.6	(0.1)	6.7	(0.1)	<0.01	<0.03

[a,b] *P* values obtained from ANCOVA analyses adjusted for age, systolic blood pressure, and heart rate ([a]), or age, systolic blood pressure, heart rate, and BMI ([b]). LVMI was not adjusted for BMI. Maximal exercise capacity adjusted for age ([a]), or age and BMI ([b]).

Table VII. Echo parameters and maximal exercise capacity during exercise test in the prediabetic subjects according to the testosterone tertiles.

Testosterone tertile	1st		2nd		3rd		P^a	P^b
LVMI (g/m^2)	108.4	(3.7)	115.9	(3.7)	110.5	(3.7)	NS	
EF (%)	63.7	(1.1)	63.0	(1.1)	66.0	(1.1)	NS	NS
E/E'	9.5	(0.3)	10.0	(0.3)	9.7	(0.3)	NS	NS
E/A	1.08	(0.04)	1.08	(0.04)	1.10	(0.04)	NS	NS
IVRT (ms)	100.2	(2.9)	104.2	(2.9)	98.4	(2.9)	NS	NS
Septal wall (cm)	11.3	(0.2)	11.4	(0.2)	11.4	(0.2)	NS	NS
Max watts during exercise test	124.7	(2.6)	124.2	(2.6)	130.7	(2.6)	NS	NS
Max METs during exercise test	5.7	(0.2)	6.0	(0.2)	6.1	(0.2)	NS	NS

[a,b] *P* values obtained from ANCOVA analyses adjusted for age, systolic blood pressure, and heart rate ([a]), or age, systolic blood pressure, heart rate, and BMI ([b]). LVMI was not adjusted for BMI. Maximal exercise capacity adjusted for age ([a]), or age and BMI ([b]).

system reactivity, and elevated fasting insulin and triglyceride levels and blood pressure. The variation of adiposity according to the testosterone levels could lead to the association between cardiac hypertrophy and testosterone levels. In our study of a large group of male subjects with coronary artery disease a correlation between total testosterone and septal wall thickness was found among diabetics before and after adjustments for BMI. The latter association persisted after further adjustment for metabolic parameters such as glucose control, triglycerides, and insulin. However, the weak association between left ventricular hypertrophy with testosterone levels was no longer significant after metabolic parameters were included in the same model. Only a few studies have investigated the association of testosterone with left ventricular mass. Some studies have suggested that testosterone could have an influence on left ventricular mass (12). The majority of previous studies on the matter have not, however, found clear correlation between low testosterone and increased left ventricular mass (37). In one study an inverse association between total testosterone and left ventricular mass was found that was independent of age but no longer present after adjusting for BMI or waist circumference (38). That study suggested that the link between total testosterone and left ventricular mass is mediated by body fat distribution. In our study the latter link may be somehow associated with the worse metabolic status among diabetics with the lowest testosterone levels. The association between low testosterone and increased septal wall thickness was independent of adiposity and metabolic parameters.

Maximal exercise capacity is one of the most powerful predictors of all-cause mortality among CAD patients (39). In the study by Koch et al. (40) total serum testosterone levels did not associate with exercise capacity in healthy volunteers. Contrary to these findings our study suggests that maximal exercise capacity expressed is associated with testosterone levels independent of confounding factors in patients with CAD. This is not an unexpected finding considering that testosterone is an anabolic agent that promotes muscle protein synthesis and hypertrophy (41). The association was most strongly seen among diabetics, although it was also evident for METs in the control population. Several studies have reported that the administration of testosterone improves lean body mass and maximal voluntary strength in healthy older men (41).

Limitations of our study include the cross-sectional design, measurement of total but not free or bioavailable testosterone levels, and measurement of a single testosterone level.

In conclusion our study supports the notion that low testosterone associates with metabolic alterations across all the groups of glucose tolerance. Plasma testosterone seems to be an independent indicator of maximal exercise capacity and septal wall thickness.

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