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ORIGINAL ARTICLE

Correlation of sex hormone and androgen receptor with diabetes mellitus in elderly men

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Abstract

Aim. To investigate sex hormone and androgen receptor (AR) levels and to evaluate their relationship with diabetes mellitus (DM) in senile men.

Methods. The cross-sectional study included 492 elderly men comprising 104 healthy subjects (mean age 71.4 ± 5.2 years), 259 subjects without DM (71.5 ± 5.0 years) and 129 DM patients (73.0 ± 6.3 years). Plasma concentrations of total testosterone (TT), free testosterone (FT), dehydroepiandrosterone sulphate, sex hormone-binding globulin (SHBG), estradiol (E_2), luteinising hormone) and follicle-stimulating hormone (FSH) were determined. AR-positive cells were measured by flow cytometry.

Results. TT concentrations were significantly lower in the DM group (13.8 ± 4.7 nmol/l) than in the healthy (17.1 ± 6.1 nmol/l) and non-diabetes groups (15.8 ± 6.0 nmol/l; all $P < 0.01$). FT, SHBG, AR-positive proportion (AR%) and AR fluorescence intensity showed a decreasing trend among the healthy, non-DM and DM groups, but the differences were not significant. TT, E_2, E_2/testosterone and SHBG were negatively correlated with blood glucose. SHBG was positively correlated and TT and AR% were negatively correlated with the course of DM. Logistic multiple regression analysis revealed that age, waist/hip ratio, FSH, SHBG and AR% are potential risk factors for DM.

Conclusions. Low levels of TT, SHBG and AR may be potential risk factors for DM in elderly men.

Keywords: *Steroid Hormones, Gonadal, receptors, androgen, diabetes mellitus*

Introduction

Patients with diabetes mellitus (DM) often experience sexual dysfunction, such as debility and erectile dysfunction [1]. Keating et al. found that androgen deprivation therapy for prostate cancer is associated with an increased risk of diabetes and cardiovascular disease [2]. Fukui et al. found that free testosterone (FT) concentrations in serum were lower in a relatively large number of Japanese patients with type 2 DM compared with healthy men for each decade of life between 40 and 69 years of age, and the incidence of insulin resistance and atherosclerosis in patients with low concentrations of endogenous androgens decreased after testosterone replacement therapy [3,4]. We have reported that elderly male patients with coronary heart disease (CHD) had low levels of dehydroepiandrosterone sulphate (DHEAS), total testosterone (TT), FT, sex hormone-binding globulin (SHBG) and androgen receptor (AR) compared with a healthy control group [5]. Ding et al. conducted a retrospective analysis of 43 clinical studies involving 6427 male subjects in 2006. They found that men with type 2 DM had significantly lower levels of plasma TT [mean difference –76.6 ng/dl; 95% CI –99.4 to –53.6 (–2.66 nmol/l; 95% CI –3.45 to –1.86)] and men with a higher TT concentration [range 449.6–605.2 ng/dl (15.6–21.0 nmol/l)] had a 42% lower risk of type 2 DM (relative risk 0.58; 95% CI 0.39–0.87) compared to those with lower concentrations [range 213.2–446.7 ng/dl (7.4–15.5 nmol/l)] [6].

Testosterone is found in three forms in the human body: FT (accounting for 2–4%), albumin-conjugated testosterone (accounting for 20–40%) and SHBG testosterone (accounting for 60–80%). Together, these make up TT. In the blood, a small proportion of TT is free and plays a biologically active role [4]. The largest proportion is combined with SHGB, so SHBG regulates the biological activity of testosterone in the blood. SHBG levels increase with age, and FT levels decrease more obviously than TT levels in elderly men. Haffner

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et al. reported that low SHBG and testosterone may constitute part of the pre-diabetic state in men, along with previously reported variables, such as higher glucose and insulin levels and obesity [7]. Stellato et al. also suggested that low levels of testosterone and SHBG play a role in the development of insulin resistance and subsequent type 2 DM [8]. Although some prospective studies have shown that low testosterone may be an independent risk factor for DM, the mechanism remains unclear. The purpose of this study was to investigate changes in serum sex hormone and AR levels in elderly diabetic men to assess the predictive value of sex hormones and other parameters for this population and to provide useful information for the prevention and treatment of DM.

Methods

Study population

This study complied with the Declaration of Helsinki. It was approved by the Scientific and Ethics Review Board of Chinese PLA General Hospital (Beijing, P.R. China). All patients provided written informed consent to be included in the study.

From May 2004 to May 2007, 794 residents were randomly selected from the Wan Shou Lu area of Beijing. We recruited 492 elderly men and divided them into a healthy control group ($n = 104$, aged 65–92 years, mean 71.4 $\pm$ 5.2 years), a non-DM control group ($n = 259$, aged 65–88 years, mean 71.5 $\pm$ 5 years) and a DM group ($n = 129$, aged 65–87 years, mean 73.0 $\pm$ 6.3 years). The DM diagnostic criteria were based on the standard established by the American Diabetes Association in 1997. Categorisation of healthy subjects was in accordance with the Chinese elderly healthy criteria recognised by the Geriatric Branch of the Chinese Medical Association in 1995. Subjects in the non-DM control group have some chronic diseases such as hypertension, CHD and so on.

The medical history of the patients was recorded in detail, including age, smoking history, history of hypertension and DM. Blood pressure was taken as the average of three consecutive measurements on the right arm when patients were in the resting state. Body weight, height, body mass index [BMI = body weight (kg)/height (m^2)] and waist/hip ratio (WHR) were also measured. The waist measurement was taken at the circumference crossing the midpoint between the lower edge of the costal arch and the upper edge of the iliac crest; the hip measurement was the largest hip circumference.

Biochemical parameters

After each patient had fasted for 12 h, blood samples of 4 ml (without anticoagulation) and 1 ml (anticoagulation with ethylenediaminetetraacetic acid) were taken from the ulnar vein between 07:30 and 08:30 a.m. The 4-ml sample was centrifuged at 3000 rev/min for 10 min and the supernatant was stored at –80°C for measurement of TT, FT, estradiol (E_2), DHEAS, SHBG, luteinising hormone (LH) and follicle-stimulating hormone (FSH). The 1-ml anticoagulated sample was used for measurement of AR within 2 h.

TT, FT, E_2, DHEAS, SHBG, LH and FSH were measured in the endocrine laboratory of the People's Liberation Army General Hospital (Beijing, P.R. China). TT, FT, DHEAS and SHBG were measured by enzyme-linked immunosorbent assay on a fully automated Triturus® analyser (Grifols Diagnostics, Barcelona, Spain) and appropriate kits from DSL (Webster, TX, USA). E_2, LH and FSH were measured by chemiluminescence on a fully automated IMMULITE® 1000 analyser and appropriate kits from DPC (Los Angeles, CA, USA). AR was measured in the Clinical Laboratory Division, People's Liberation Army General Hospital. Using indirect immunofluorescence labelling, a fluorescence-activated cell sorting (FACS) flow cytometer (BD Biosciences, San Jose, CA, USA) was used to detect AR levels as the mean fluorescence intensity of peripheral white blood cells. The AR-positive proportion (AR%) is the calculated value by the FACS flow cytometer – the control value. Fasting blood glucose and lipids were measured on a model 747 automatic biochemical analyser (Hitachi, Tokyo, Japan).

Statistical analysis

SPSS 11.5 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The χ^2 test was used to compare categorical variables between two groups. After a normality test, measurement data that did not follow a normal distribution were reanalysed. Results are presented as mean $\pm$ standard deviation. Student's *t*-test was used to compare measurement data between two groups. Analysis of covariance was used to correct covariate factors. The relationship between variables was assessed using correlation analysis, multiple logistic regression analysis and multiple regression analysis.

Results

General clinical features

There were more DM patients with CHD, hypertension, smoking history and a family history of DM than in the other two groups. DM patients had higher BMI and WHR than subjects in the healthy control group ($P < 0.05$). Fasting blood glucose, triglyceride, cholesterol and low-density lipoprotein cholesterol tended to increase in the following order: healthy controls < non-DM control group < DM group, but high-density lipoprotein cholesterol showed the opposite trend. The differences were not statistically significant. Compared with the healthy control group, significantly more non-DM control subjects suffered from CHD, hypertension and other chronic diseases (Table I).

Table I. Comparison of general clinical features, sex hormones and AR among the groups.

Parameter	Healthy control group	Non-DM control group	DM group
n	104	259	129
Age (yr)	71.38 ± 5.15	71.57 ± 5.00	72.93 ± 6.34
CHD [*n* (%)]	0 (0.00)	40 (15.44)	47 (36.43)†§
Hypertension [*n* (%)]	0 (0.00)	137 (52.90)	80 (62.02)⋆
Smoking history [*n* (%)]	51 (49.03)	134 (51.74)	98 (75.97)†§
Family history of DM [*n* (%)]	1 (0.00)	6 (2.24)	14 (10.86)†§
DM duration	0	0	10.44 ± 8.18
BMI (kg/m^2)	24.49 ± 2.80	25.22 ± 3.14	25.34 ± 2.45⋆
WHR	0.88 ± 0.06	0.89 ± 0.06	0.90 ± 0.05⋆
Systolic blood pressure (mm Hg)	130.03 ± 16.69	136.57 ± 19.75	133.78 ± 20.67
Diastolic blood pressure (mm Hg)	77.21 ± 9.34	78.91 ± 10.91	76.55 ± 12.58
TG (mmol/l)	1.23 ± 0.79	1.27 ± 0.73	1.41 ± 0.65
TC (mmol/l)	4.86 ± 0.82	4.91 ± 0.85	4.92 ± 0.86
HDL-c (mmol/l)	1.29 ± 0.31	1.28 ± 0.30	1.25 ± 0.29
LDL-c (mmol/l)	3.04 ± 0.75	3.05 ± 0.75	3.10 ± 0.66
Glucose (mmol/l)	5.88 ± 0.96	6.00 ± 1.61	8.01 ± 21.12
LH (U/l)	8.36 ± 4.94	8.90 ± 13.60	9.82 ± 6.17
FSH (U/l)	13.36 ± 4.57	13.54 ± 9.79	15.96 ± 11.32
TT (nmol/l)	17.10 ± 6.14	15.89 ± 6.07	13.84 ± 4.72†§
E_2 (pmol/l)	95.38 ± 49.78	95.71 ± 6.077	95.90 ± 41.46
FT (pmol/l)	10.51 ± 4.11	9.96 ± 3.78	9.81 ± 4.31
SHBG (nmol/l)	186.06 ± 89.07	176.00 ± 88.27	165.00 ± 96.09
DHEA-s (μg/l)	821.07 ± 594.51	881.16 ± 890.41	895.00 ± 882.72
E_2/T	5.75 ± 2.69	6.33 ± 3.41	7.37 ± 3.47†‡
AR-positive rate (%)	67.67 ± 21.19	64.51 ± 21.55	64.82 ± 19.13
AR fluorescence intensity	3.36 ± 1.05	3.21 ± 0.96	3.17 ± 0.91

⋆$P < 0.05$, †$P < 0.01$ vs. healthy group; ‡$P < 0.05$, §$P < 0.01$ vs. non-DM group.

Hormone and AR levels

Because CHD, hypertension, smoking history, family history of DM, BMI and WHR differed among the three groups, these parameters were defined as covariates. After factor correction by covariance analysis, TT levels in the DM group were lower than in the two control groups ($P < 0.01$), and the E_2/testosterone (T) ratio was higher ($P < 0.01$ vs. healthy and $P < 0.05$ vs. non-DM). LH, FSH, E_2 and DHEAS tended to increase in the following order: healthy controls < non-DM control group < DM group, but FT, SHBG, the AR% and the AR fluorescence intensity showed the opposite trend. The differences were not statistically significant (Table I).

Multiple regression analysis of the clinical data, sex hormone levels, AR and blood glucose

Multiple regression analysis was performed with blood glucose as the dependent variable, and age, BMI, WHR, systolic blood pressure, diastolic blood pressure, LH, FSH, TT, E_2, FT, SHBG, DHEAS, E_2/T and AR as the independent variables. Analysis revealed that TT, E_2, E_2/T and SHBG were negatively correlated with blood glucose, whereas FSH was positively correlated (Table II).

Correlation analysis of clinical data, sex hormones, AR and DM duration

Multiple logistic regression for all 492 patients was carried out using DM duration as the dependent variable, and age, smoking history, BMI, WHR, systolic blood pressure, diastolic blood pressure, LH, FSH, TT, FT, SHBG, E_2, E_2/T, DHEAS and AR as the independent variables. Analysis revealed that smoking history and SHBG were positively correlated with DM duration, TT and AR% were negatively correlated, and the average AR fluorescence intensity showed no correlation (Table III).

Multiple regression analysis of sex hormone, AR and DM risk factors

Multiple regression analysis with sex hormones and AR as the independent variables and DM risk factors as the dependent variables revealed that age, CHD history, smoking history, WHR, diastolic blood pressure, FSH, SHBG and AR% are DM risk factors (Table IV).

Discussion

It is now well accepted that DM is related to disorders of sex hormone metabolism. The Endocrine Society Clinical Practice Guidelines recommend that serum testosterone should be measured in men with type 2 DM because of the prevalence of low serum testosterone in this population [9]. Many studies have revealed a correlation between sex hormones and DM in elderly men. One cross-sectional study including 746 men (of whom 116 were diabetic) revealed that TT levels were below normal in 34% of DM and 23% of non-DM subjects [10]. The Massachusetts Male Aging Study

Table II. The multiple regression analysis of the clinical data, sex hormone levels, AR and blood glucose.

	B	*β*	*t*	*P*
Age (years)	−0.164	−0.068	−1.083	0.280
BMI (kg/m^2)	0.441	0.105	1.564	0.119
WHR	−16.628	−0.073	−1.144	0.254
Systolic blood pressure (mm Hg)	−0.039	−0.062	−0.906	0.366
Diastolic blood pressure (mm Hg)	0.008	0.007	0.099	0.921
LH (U/l)	−0.007	−0.007	−0.128	0.898
FSH (U/l)	0.255	0.205	3.343	0.001
TT (nmol/l)	−1.527	−0.718	−5.636	0.000
E_2 (pmol/l)	−0.160	−0.618	−4.223	0.000
FT (pmol/l)	−0.149	−0.046	−0.767	0.444
SHBG (nmol/l)	−0.039	−0.277	−3.792	0.000
DHEA-S (μg/ml)	0.000	−0.009	−0.153	0.878
E_2/T	−1.536	−0.418	−3.153	0.002
AR-positive proportion	0.010	0.016	0.184	0.854
AR fluorescence intensity	0.058	0.004	0.050	0.960

B refers to standard regression coefficient.

Table III. The correlation analysis of clinical data, sex hormones, AR and duration of diabetes.

	B	*β*	*t*	*P*
Age (years)	0.097	0.096	1.447	0.149
Smoking history	0.037	0.133	2.253	0.025
BMI (kg/m^2)	0.046	0.026	0.248	0.804
WHR	0.283	0.561	0.785	0.433
Systolic blood pressure (mm Hg)	−0.001	−0.006	−0.079	0.937
Diastolic blood pressure (mm Hg)	−0.066	−0.139	−1.953	0.052
LH (U/l)	0.002	0.006	0.096	0.924
FSH (U/l)	0.031	0.059	0.933	0.352
TT (nmol/l)	−0.149	−0.165	−2.260	0.025
FT (pmol/l)	0.033	0.024	0.379	0.705
SHBG (nmol/l)	0.009	0.146	1.956	0.051
E_2 (pmol/l)	−0.130	−0.321	−0.890	0.211
E_2/T	0.233	0.150	2.426	0.016
DHEA-S (ng/ml)	0.000	−0.036	−0.626	0.532
AR-positive rate (%)	−0.028	0.008	12.887	0.000
AR fluorescence intensity	−0.467	−0.083	−0.921	0.358

Table IV. The multiple regression analysis of sex hormones, AR and risk factors of diabetes.

	B	SE	Wald $\chi 2$	*P*
Age (years)	0.071	0.027	7.038	0.008
History of hypertension	0.275	0.389	0.500	0.480
History of coronary heart disease	1.177	0.463	6.466	0.011
Smoking history	0.023	0.009	5.776	0.016
BMI (kg/m^2)	0.578	1.040	0.309	0.578
WHR	8.215	3.157	6.773	0.009
Systolic blood pressure (mm Hg)	0.006	0.012	0.310	0.578
Diastolic blood pressure (mm Hg)	−0.030	0.015	3.929	0.047
LH (U/l)	0.005	0.014	0.137	0.711
FSH (U/l)	0.035	0.017	4.080	0.043
FT (pmol/l)	−0.003	0.048	0.004	0.947
SHBG (nmol/l)	−0.009	0.002	19.630	0.000
TT (nmol/l)	0.110	0.074	2.222	0.136
E_2 (pmol/l)	−0.010	0.010	0.993	0.319
DHEA-S (μg/ml)	0.000	0.000	0.187	0.666
E_2/T	0.028	0.105	0.071	0.790
AR-positive proportion	−0.028	0.008	12.887	0.000
AR fluorescence intensity	−0.087	0.651	0.018	0.894

B refers to partial regression coefficient.

showed unadjusted associations between type 2 DM and both low testosterone and low SHBG in ageing men [11]. In an 11-year follow-up of 702 Finnish men, Laaksonen et al. found that subjects with TT, calculated FT and SHBG levels in the lower quartile had a several-fold increased risk of developing metabolic syndrome (Odds ratio 2.3, 95% CI 1.5–3.4; 1.7, 1.2–2.5 and 2.8, 1.9–4.1, respectively) and DM (2.3, 1.3–4.1; 1.7, 0.9–3.0 and 4.3, 2.4–7.7, respectively) after adjustment for age [12]. This is in agreement with our results indicating that TT levels were lower in the DM group than in the two control groups and were negatively correlated with DM duration. It is considered that changes in sex hormone levels in diabetic men may be correlated to a decrease in testicular secretion or an increase in testosterone transformation in the peripheral circulation. Elevated blood glucose may directly affect testicular function or influence the liver clearance rate of testosterone. Premature ageing of gonadal endocrine cells may be another factor. Clinically, a patient suffering from gonadal dysfunction and type 2 DM is usually obese. With increasing BMI, the symptoms of gonadal dysfunction become increasingly obvious. Isidori et al. confirmed that fasting insulin levels, the insulin resistance index and C-peptide levels were higher in patients with BMI $>$ 30 kg/m^2 than in patients with BMI $<$ 30 kg/m^2, whereas serum testosterone levels showed the trend [13]. In our study, BMI and WHR were significantly higher in the DM group than in the control groups, whereas TT levels were lower and FT levels showed a decreasing trend in the DM group. A high level of testosterone within the physiological range can inhibit lipoprotein lipase activity, reduce fat mass and increase muscle content, and thus improve insulin resistance [14]. At the same time, obesity, especially central obesity, often coexists with DM and can decrease FT and TT levels. The specific mechanism may be that obesity increases male glucocorticoid production and metabolism. In addition, obesity is accompanied by overexpression of 11β-hydroxysteroid dehydrogenase type 1. This enzyme converts biologically inactive cortisone to cortisol, which also binds with high affinity to the gluco- and mineralocorticoid receptors in humans. All these changes contribute to dysfunction of the hypothalamic–pituitary–adrenal axis and gonadal dysfunction [15,16].

Our study showed that TT and SHBG levels were negatively correlated with blood glucose. Boyanov et al. confirmed that testosterone supplementation therapy for 3 months significantly improved metabolic control,

with decreases in blood glucose and mean glycated haemoglobin (from 10.4% to 8.6%) [17]. Shahani et al. found that prostate cancer patients who received 3–6 months of testosterone therapy after castration were prone to early metabolic changes and hyperinsulinemia, and those who received more than 12 months of therapy were prone to a higher incidence of metabolic syndrome [18].

When exogenous testosterone is supplied, insulin sensitivity and glucose metabolism are enhanced and improvements in CHD symptoms occur. This suggests that testosterone can increase insulin sensitivity and improve insulin resistance. Pitteloud et al. observed a strong positive correlation between insulin sensitivity and the testosterone response to human chorionic gonadotropin (hCG) [19]. Currently, it is speculated that the mechanisms by which insulin resistance leads to a decrease in testosterone levels are as follows. (1) A decrease in and loss of Leydig cells occur due to insulin stimulation. (2) High blood glucose leads to a decrease in testosterone release by inhibiting pituitary LH release. (3) Leptin is negatively correlated with testosterone levels. Leptin may decrease testosterone levels by inhibiting the function of Leydig cells, increasing leptin receptor levels in Leydig cells and inhibiting hCG-induced testosterone secretion [20,21]. (4) Tumour necrosis factor-α can decrease testosterone levels by inhibiting steroidogenesis in Leydig cells at the transcriptional level [22]. (5) Decreased maximal aerobic capacity (V_{O2max}) and decreased expression of mitochondrial genes involved in oxidative phosphorylation may be factors in the decrease in testosterone levels [23].

This study shows that AR expression decreased in elderly male DM patients and AR% was negatively correlated with DM duration. Thus, AR% is a potential DM risk factor. The reason for abnormal AR expression caused by DM may be twofold: (1) the structure and function of Leydig cells are damaged and testosterone levels decrease due to a decrease in synthesis, leading to reduced regulation of AR expression; and (2) disorder of protein metabolism caused by DM affects normal AR synthesis. Conversely, Fan et al. showed that AR-null male mice ($AR^{L-/Y}$) were less dynamic and had lower oxygen consumption compared with wild-type males ($AR^{X/Y}$) [24]. They observed that inactivation of the androgen–AR system in male rats led to a chronic positive energy balance and contributed to an accelerated increase in fat content and obesity. When body mass significantly increased, accompanied by an increase in hormone-sensitive lipase transcription, the transcription of fat synthesis genes did not change significantly. Lipolysis of testosterone occurred. When the AR is blocked, inhibition of testosterone lipolysis results in an increase in fat content. In this study, although TT levels were lower in DM patients, there was no significant difference in AR levels compared with the control group. It is inferred that when testosterone levels in DM patients are low, there may be a negative feedback regulation to increase body weight to maintain physiological functions.

Decreases in TT and low levels of TT, SHBG and AR may be potential DM risk factors in elderly men. Low androgen and AR levels in elderly men may be involved in the incidence and development of DM via interaction with obesity, glucose homeostasis, insulin resistance and multiple cytokines, but the specific mechanism and the causality still need to be confirmed by further clinical and basic research.

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References

1. Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. Aging Male 2007;10:189–196.
2. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–4456.
3. Fukui M, Soh J, Tanaka M, Kitagawa Y, Hasegawa G, Yoshikawa T, Miki T, Nakamura N. Low serum testosterone concentration in middle-aged men with type 2 diabetes. Endocr J 2007;54:871–877.
4. Saad F, Gooren L. The role of testosterone in the metabolic syndrome: a review. J Steroid Biochem Mol Biol 2009;114:40–43.
5. Cao J, Zou H, Zhu BP, Wang H, Li J, Ding Y, Li XY. Sex hormones and androgen receptor: risk factors of coronary heart disease in elderly men. Chin Med Sci J 2010;25:44–49.
6. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2006;295:1288–1299.
7. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. Mrfit research group. Multiple risk factor intervention trial. Am J Epidemiol 1996;143:889–897.
8. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the massachusetts male aging study. Diabetes Care 2000;23:490–494.
9. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91: 1995–2010.
10. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int 2005;96:867–870.
11. O' Donnell AB, Araujo AB, McKinlay JB. The health of normally aging men: the massachusetts male aging study (1987–2004). Exp Gerontol 2004;39:975–984.
12. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036–1041.

13. Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673–3680.
14. Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens. J Clin Endocrinol Metab 1995;80:239–243.
15. Davani B, Khan A, Hult M, Martensson E, Okret S, Efendic S, Jörnvall H, Oppermann UC. Type 1 11beta -hydroxysteroid dehydrogenase mediates glucocorticoid activation and insulin release in pancreatic islets. J Biol Chem 2000;275:34841–34844.
16. Dötsch J, Rascher W. The role of 11beta-hydroxysteroid dehydrogenase activity in the metabolic syndrome: lessons learned from the animal model. Eur J Endocrinol 2002;146:603–605.
17. Boyanov MA, Boneva Z, Christov VG.Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003;6:1–7.
18. Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. J Clin Endocrinol Metab 2008;93:2042–2049.
19. Pitteloud N Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in leydig cell testosterone secretion in men. J Clin Endocrinol Metab 2005;90:2636–2641.
20. Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 2008;93:784–791.
21. Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, Fabbri A. Expression of functional leptin receptors in rodent leydig cells. Endocrinology 1999;140:4939–4947.
22. Hong CY, Park JH, Ahn RS, Im SY, Choi HS, Soh J, Mellon SH, Lee K. Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha. Mol Cell Biol 2004;24:2593–2604.
23. Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 2005;28:1636–1642.
24. Fan W, Yanase T, Nomura M, Okabe T, Goto K, Sato T, Kawano H, Kato S, Nawata H. Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. Diabetes 2005; 54(4):1000–1008.