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CLINICAL STUDY

# Sex hormones, inflammation and the metabolic syndrome: a population-based study

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## Abstract

*Objective*: Mild hypoandrogenism in men is associated with features of the metabolic syndrome, but the association with the metabolic syndrome itself using an accepted definition has not been described.

*Design*: Men with the metabolic syndrome were identified and testosterone and sex hormone-binding globulin (SHBG) levels were determined in a population-based cohort of 1896 non-diabetic middle-aged Finnish men.

*Results*: Calculated free testosterone and SHBG were 11% and 18% lower ($P < 0.001$) in men with the metabolic syndrome ($n = 345$, World Health Organisation definition). After categorisation by tertiles and adjusting for age and body mass index, total and free testosterone and SHBG were inversely associated with concentrations of insulin, glucose, triglycerides, C-reactive protein (CRP) and CRP-adjusted ferritin and positively associated with high-density lipoprotein cholesterol. Men with free testosterone levels in the lowest third were 2.7 (95% confidence interval (CI) 2.0–3.7) times more likely to have the metabolic syndrome in age-adjusted analyses, and 1.7 (95% CI 1.2–2.4) times more likely even after further adjusting for body mass index. Exclusion of men with cardiovascular disease did not alter the association. The inverse association of SHBG with the metabolic syndrome was somewhat stronger.

*Conclusions*: Low testosterone and SHBG levels were strongly associated not only with components of the metabolic syndrome, but also with the metabolic syndrome itself, independently of body mass index. Furthermore, sex hormones were associated with inflammation and body iron stores. Even in the absence of late-stage consequences such as diabetes and cardiovascular disease, subtle derangements in sex hormones are present in the metabolic syndrome, and may contribute to its pathogenesis.

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## Introduction

Low levels of male sex hormones have quite consistently been associated with components of the metabolic syndrome. The metabolic syndrome is a concurrence of insulin resistance, mild dyslipidaemia, hypertension and visceral obesity that substantially increases the risk for cardiovascular disease and type 2 diabetes (1–5). The syndrome is characterised by overweight and insulin resistance, and is also known as the insulin resistance syndrome. The pathogenesis of this syndrome has multiple origins, but obesity, sedentary lifestyle, diet and other unknown factors, some genetic, clearly interact to produce it (2, 3, 6, 7).

In cross-sectional studies, low concentrations of testosterone and sex hormone-binding globulin (SHBG) have been associated with visceral obesity, insulin resistance or hyperinsulinaemia and dyslipidaemia (8–12). The association of testosterone and SHBG with an altered lipid profile is partly secondary to abdominal fat accumulation, but there also appears to be an independent relationship between low levels of testosterone and hyperinsulinaemia (9, 11, 12) and dyslipidaemia (13). Low levels of testosterone have also predicted the worsening abdominal obesity (14) and development of diabetes in men (15–17). The association of dehydroepiandosterone levels with components of the metabolic syndrome in men is inconsistent, but some studies suggest that low dehydroepiandosterone levels are associated with impaired glucose tolerance and insulin resistance (11).

 

Testosterone itself may have a causal role in the pathogenesis of the metabolic syndrome or its components by increasing muscle mass, decreasing abdominal obesity and improving insulin sensitivity (18). The effect of weight loss on free and total testosterone and SHBG has been poorly described, but overall abdominal obesity increases glucocorticoid turnover and production, resulting in abnormal regulation of the hypothalamic–pituitary–adrenal axis (19, 20) and possibly mild hypoandrogenism in men. Few population-based studies have assessed the association of sex hormones and SHBG with components of the metabolic syndrome. The association of testosterone and SHBG levels with the metabolic syndrome itself using accepted definitions has not previously been reported. In this cross-sectional study we examined the role of testosterone, SHBG and dehydroepiandosterone sulphate (DHEAS) levels with the metabolic syndrome itself, its components and factors related to it in 1896 non-diabetic middle-aged Finnish men.

## Subjects and methods

The subjects were participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), which is an ongoing prospective population-based study designed to investigate risk factors for chronic diseases, including type 2 diabetes and cardiovascular diseases, among middle-aged men (21). The study population was a random age-stratified sample of men living in Eastern Finland who were 42, 48, 54 or 60 years old at baseline examinations in 1984–1989. The Research Ethics Committee of the University of Kuopio approved the study. All study subjects gave their written informed consent. The recruitment of the subjects has been described previously in detail (21). The present study included 1896 non-diabetic men who had complete data on sex hormones and the main characteristics of the metabolic syndrome.

### *Measurement of sex hormones and SHBG*

Sex hormone-binding globulin was determined using a 1235 AutoDELFIA automatic system based on a time-resolved fluoroimmunoassay (AutoDELFIA SHBG, Wallac Co., Turku, Finland). Total testosterone levels were measured with the AutoDELFIATestosterone kit (Wallac Co.). We considered a concentration of total testosterone of $<11$ nmol/l to represent clinical hypogonadism (22). We also defined a level of calculated free testosterone of 160 pmol/l (the lower limit of the normal range at our hospital) as the cut-off for clinical hypogonadism. Non-SHBG-bound, free testosterone (fT) was obtained using the following formula: proportion (%) of fT (fT%) = 2.28−1.38*log(SHBG nmol/1/10), and serum fT (pmol/l) = fT%*T (nmol/l)*10.

### *Assessment of components of or features related to the metabolic syndrome*

Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m$^2$). Waist circumference was taken as the average of two measurements taken after inspiration and expiration at the midpoint between the lowest rib and the iliac crest. The waist-hip ratio (WHR) was defined as the ratio of waist girth to the circumference of the hips measured at the trochanter major.

Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley, UK). The measurement protocol included three measurements in the supine, one in the standing and two in the sitting position with 5-min intervals. The mean of all six measurements was used as systolic and diastolic blood pressure.

Subjects were asked to fast for 12 h before blood sampling. They were also asked to refrain from smoking for 12 h and from consuming alcohol for three days before blood draws. Blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). The coefficient of variation (CV) was 8.9% at 9.4 pmol/l. High-density lipoprotein (HDL) fractions were separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically. The CV was 9.2% for HDL ($n = 210$) and 1.9% for triglycerides ($n = 7$). Fibrinogen was measured based on the clotting of diluted plasma with excess thrombin. The CV was 2.4%. Serum C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity CR assay, DPC, Los Angeles, CA, USA). Serum non-esterified fatty acids were determined chromatographically without pre-separation (23, 24). Fatty acids were chromatographed in an NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett Packard 5890 Series II gas chromatograph (Avondale, PA, USA) with a flame ionisation detector.

Serum ferritin was measured with a radioimmunoassay (Amersham International) based on a double-antibody technique as described previously (25). Because ferritin is also an acute phase reactant, we adjusted ferritin concentrations by CRP levels before statistical analyses to reduce the influence of inflammation on ferritin levels.

### *Definition of the metabolic syndrome*

The metabolic syndrome was defined as the presence of hyperinsulinaemia (fasting serum insulin concentration in the top 25% of these non-diabetic men), impaired fasting glucose, or diabetes and the presence of at least two of the following: abdominal obesity (WHR $>0.90$ or BMI $\geq 30$ kg/m$^2$), dyslipidaemia

(serum triglycerides $\geq 1.70$ mmol/l or serum HDL cholesterol $< 0.9$ mmol/l), or hypertension (blood pressure $\geq 140/90$ mmHg or blood pressure medication) (26). Impaired fasting glucose was defined as a fasting blood glucose of 5.6–6.0 mmol/l, equivalent to a plasma glucose of 6.1–6.9 mmol/l (26). Diabetes was defined as fasting blood glucose concentration $\geq 6.1$ mmol/l (equivalent to plasma glucose $\geq 7.0$ mmol/l) or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment (26). In the present study men with diabetes were excluded.

The World Health Organisation (WHO) definition of the metabolic syndrome proposed that insulin resistance be measured by the euglycaemic hyperinsulinaemic clamp method and that impaired glucose tolerance be used in the definition (26). In the present study, fasting serum insulin concentration was used to estimate insulin resistance, and impaired fasting glucose was used as a substitute for impaired glucose tolerance, as has been proposed for epidemiological studies (27). Microalbuminuria as a core component in the metabolic syndrome is controversial (27) and uncommon in non-diabetic persons (28); microalbuminuria was therefore not included in the present definition (27). These modifications of the WHO definition of the metabolic syndrome have been validated (4, 5). We also used the National Cholesterol Education Program (NCEP) definition as a confirmatory analysis (4, 29).

### *Other assessments*

Assessments of medical history and medications, smoking, alcohol consumption and adult socioeconomic status have been described previously (30).

### *Statistical analyses*

Differences in clinical and biochemical characteristics between men who had the metabolic syndrome and those who did not were tested for statistical significance with Student's *t*-test, and where indicated, the chi-squared test. Concentrations of sex hormones and SHBG were categorised into thirds to assess the cross-sectional association with components of or variables related to the metabolic syndrome using ANCOVA. The linear association of androgen and SHBG concentrations was also assessed with linear regression using continuous variables. The associations of androgens and SHBG with the metabolic syndrome was estimated using logistic regression models adjusting for covariates. The covariates for the logistic regression models were forced into the model. Variables are given as means±S.D., except for variables with a skewed distribution (DHEAS, SHBG, insulin, triglycerides, CRP-adjusted ferritin), which are given as medians and interquartile ranges. In analyses using continuous variables, these variables were log transformed. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 11.0 for Windows (Chicago, IL, USA).

## Results

### *Characteristics according to the presence of the metabolic syndrome*

Men with the metabolic syndrome as defined by the WHO had 19%, 11% and 18% lower levels of total testosterone, calculated free testosterone and sex hormone-binding globulin than men without the syndrome (Table 1). In the 345 men with the metabolic syndrome, 51 (17%) and 18 (6%) had clinical hypogonadism as defined by total and free testosterone levels respectively. Corresponding values in the 1551 men without the metabolic syndrome were 68 (4%) and 25 (2%) ($P < 0.001$ for the difference between men with and without the metabolic syndrome). DHEAS levels were similar in both groups. As would be expected, men with the metabolic syndrome had a larger waist girth and a higher BMI and WHR, higher fasting blood glucose and serum insulin, higher serum triglycerides and lower serum HDL cholesterol, and higher blood pressure. Men with the metabolic syndrome also had higher fibrinogen, CRP, CRP-adjusted ferritin and haemoglobin levels than men without the syndrome.

### *Association of sex hormones with components of the metabolic syndrome*

Sex hormones were categorised into thirds to assess the association of sex hormones with components of the metabolic syndrome after adjustment for age and BMI. The linear association was also assessed with continuous variables. Low total and free testosterone levels were associated with high levels of insulin, glucose and triglycerides and low levels of HDL cholesterol (Table 2; for all, $P < 0.001$ for both the effect and the linear trend). Total and free testosterone were also inversely associated with CRP concentrations ($P < 0.05$ for the effect and $P < 0.001$ for the trend). Testosterone levels had similar associations, although somewhat weaker. SHBG concentrations were also strongly associated with components of the metabolic syndrome, including blood pressure, and to a lesser degree, positively with fibrinogen but inversely with CRP levels. The positive association of SHBG with fibrinogen levels was partly influenced by BMI, because in age-adjusted analyses, the association was no longer significant ($P = 0.085$). DHEAS levels were positively associated with HDL levels, but also positively with glucose, blood pressure, fibrinogen, and CRP concentrations. SHBG and sex hormones were inversely associated with CRP-adjusted ferritin. Free and total testosterone were positively associated with haemoglobin levels. These associations persisted even

**Table 1** Characteristics of the 1896 non-diabetic middle-aged men according to the presence of the metabolic syndrome. Values are presented as means±S.D., medians (interquartile ranges) or percentages.

| | − Metabolic syndrome | + Metabolic syndrome | *P* |
|---|---|---|---|
| Number | 1551 | 345 | |
| Age (years) | 52.5±5.7 | 53.4±5.6 | 0.005 |
| Smokers (%) | 32.8 | 27.9 | 0.080 |
| Alcohol consumption (g/wk) | 75±137 | 89±146 | 0.54 |
| Adult socioeconomic status | 8.1±4.2 | 8.4±4.2 | 0.24 |
| Blood pressure medication (%) | 15 | 49 | <0.001 |
| Systolic blood pressure (mmHg) | 130.7±15.2 | 141.0±18.1 | <0.001 |
| Diastolic blood pressure (mmHg) | 87.0±9.9 | 93.5±10.7 | <0.001 |
| BMI (kg/m$^2$) | 26.1±3.0 | 29.8±3.6 | <0.001 |
| Waist girth (cm) | 88.9±8.6 | 98.9±9.8 | <0.001 |
| WHR | 0.94±0.06 | 0.99±0.06 | <0.001 |
| Fasting serum insulin (mU/l) | 8.8 (6.9–10.8) | 16.4 (14.2–16.9) | <0.001 |
| Fasting blood glucose (mmol/l) | 4.5±0.4 | 4.8±0.5 | <0.001 |
| Serum HDL cholesterol (mmol/l) | 1.33±0.30 | 1.14±0.24 | <0.001 |
| Serum triglycerides (mmol/l) | 1.03 (0.76–1.42) | 1.82 (1.25–2.44) | <0.001 |
| C-reactive protein (mg/l) | 1.13 (0.64, 2.17) | 1.24 (0.69, 2.35) | <0.001 |
| Fibrinogen (g/l) | 2.98±0.57 | 3.18±0.59 | <0.001 |
| Haemoglobin (g/l) | 146±8.9 | 151±10.0 | <0.001 |
| Non-esterified free fatty acids (mmol/l) | 481 (398, 588) | 555 (446, 677) | <0.001 |
| CRP-adjusted ferritin (μg/l) | 117 (70, 191) | 188 (110, 310) | <0.001 |
| Serum total testosterone (nmol/l) | 21.6±7.4 | 17.6±6.8 | <0.001 |
| Serum calculated free testosterone (pmol/l) | 307±75 | 273±79 | <0.001 |
| Serum SHBG (nmol/l) | 38.1 (28.9–50.0) | 31.2 (23.0–40.6) | <0.001 |
| Serum DHEAS (μmol/l) | 3.87 (2.71–5.34) | 3.76 (2.43–5.61) | 0.41 |

HDL, high-density lipoprotein.

when there were further adjustments for smoking (not shown).

## *Association of sex hormones with the metabolic syndrome*

Men with concentrations of total testosterone and SHBG in the lower third were about 3.5-fold more likely to have the metabolic syndrome as defined by the WHO than men with levels in the upper third, even after adjustment for age and other confounders such as smoking, alcohol intake, socioeconomic status and presence of cardiovascular disease (Table 3). Similarly, men with free testosterone levels in the lower third were 2.7–2.8 times more likely to have the metabolic syndrome. The associations of total and free testosterone and SHBG remained highly significant even after adjusting further for BMI (odds ratios 1.7–1.9 for upper vs lower third). No clear association with DHEAS was seen.

In analyses using clinically applicable dichotomous cut-offs for hypogonadism, total testosterone levels less than 11 were also associated with the metabolic syndrome (model 2 from Table 3, total testosterone: odds ratio (OR) 3.72, 95% confidence interval (CI) 2.50–5.52; free testosterone: OR 3.14, 95% CI 1.67–5.92). The association was no longer significant for free testosterone after further adjustment for BMI (model 3, total testosterone: OR 1.88, 95% CI 1.18–2.98; free testosterone: OR 1.72, 95% CI 0.79–3.75).

In analyses using the NCEP definition of the metabolic syndrome, the associations were similar to analyses using the WHO definition (e.g. model 2 from Table 3, upper vs lower third, total testosterone: OR 4.77, 95% CI 3.11–7.30; free testosterone: OR 3.49, 95% CI 2.35–5.16; SHBG: OR 4.54, 95% CI 2.93–7.04; model 3, upper vs lower third, total testosterone: OR 2.42, 95% CI 1.53–3.82; free testosterone: OR 2.04, 95% CI 1.33–3.11; SHBG: OR 2.41, 95% CI 1.51–3.84).

## *Analyses in men without cardiovascular disease*

We also repeated the analyses in men who not only did not have diabetes, but also did not have cardiovascular disease. The overall effect of sex hormones and SHBG on components of the metabolic syndrome or related variables was qualitatively similar to those shown in Table 2. Exceptions included blood glucose, blood pressure and C-reactive protein, in which the effect no longer reached statistical significance. The linear trend for the association of sex hormones and SHBG with components of the metabolic syndrome was also for the most part similar to those shown in Table 2. Exceptions included blood pressure, fibrinogen and C-reactive protein, in which the association was not significant.

Associations of low testosterone and SHBG levels with the metabolic syndrome in men without cardiovascular disease were similar to those shown in Table 3, even when adjusted for BMI (model 3, lower vs upper third, total testosterone: OR 1.96, 95% CI 1.23–3.09; free testosterone: OR 1.67, 95% CI 1.03–2.70, SHBG: OR 1.66, 1.03–2.67).

**Table 2** Age- and BMI-adjusted effects of sex hormone concentrations on core or related features of the metabolic syndrome in 1896 men without diabetes.

| | WHR | Insulin | Glucose | HDL-cholesterol | Triglycerides | Non-esterified fatty acids | SBP | BP medication | Fibrinogen | hs-CRP | CRP-adjusted ferritin | Hb |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total testosterone** (nmol/l) | | | | | | | | | | | | |
| 1.1–16.9 | 0.95 | 12.0[c,f] | 4.63[c,f] | 1.26[c,f] | 1.50[c,f] | 546[c,f] | 132.7[f] | 19 | 2.99 | 2.84[a,f] | 176[a,f] | 146[c,f] |
| 17.0–23.3 | 0.94 | 10.5 | 4.56 | 1.28 | 1.32 | 510 | 132.4 | 22 | 2.99 | 2.23 | 161 | 148 |
| 23.4–51.7 | 0.94 | 10.4 | 4.51 | 1.33 | 1.20 | 509 | 131.5 | 18 | 3.02 | 2.04 | 159 | 148 |
| **Free testosterone** (pmol/l) | | | | | | | | | | | | |
| 10–265 | 0.95 | 11.8[b,f] | 4.61[b,f] | 1.27[f] | 1.45[b,f] | 555[c,f] | 132.1[c] | 19 | 3.01 | 2.85[a,f] | 173[d] | 146[c,f] |
| 266–331 | 0.94 | 10.6 | 4.56 | 1.29 | 1.30 | 508 | 133.0 | 20 | 2.98 | 2.06 | 162 | 147 |
| 332–717 | 0.95 | 10.6 | 4.53 | 1.31 | 1.27 | 501 | 131.6 | 20 | 3.01 | 2.22 | 159 | 148 |
| **SHBG** (nmol/l) | | | | | | | | | | | | |
| 4.6–30.5 | 0.95 | 11.7[c,f] | 4.63[c,f] | 1.27[c,f] | 1.53[c,f] | 529 | 133.0[c,f] | 20 | 2.94[b] | 2.52[f] | 175[a,e] | 146[a] |
| 30.6–43.7 | 0.94 | 10.7 | 4.55 | 1.27 | 1.29 | 510 | 132.1 | 22 | 3.01 | 2.42 | 154 | 148 |
| 43.8–131.9 | 0.94 | 10.5 | 4.52 | 1.34 | 1.1 | 526 | 131.3 | 18 | 3.07 | 2.18 | 167 | 147 |
| **DHEAS** (μmol/l) | | | | | | | | | | | | |
| 0.80–3.10 | 0.94 | 11.2 | 4.55[a,e] | 1.26[b,f] | 1.39[d] | 516[e] | 131.3[a,e] | 23 | 2.96[e] | 2.22[a,d] | 162[c,f] | 147 |
| 3.11–4.78 | 0.94 | 10.6 | 4.55 | 1.29 | 1.32 | 519 | 131.6 | 18 | 3.01 | 2.34 | 147 | 147 |
| 4.79–16.0 | 0.95 | 11.2 | 4.61 | 1.32 | 1.32 | 530 | 133.5 | 19 | 3.03 | 2.58 | 186 | 148 |

HDL, high-density lipoprotein; SBP, systolic blood pressure; BP, blood pressure; hs-CRP, high sensitivity C-reactive protein; Hb, haemoglobin; SHBG, sex hormone binding globulin; DHEAS, dehydroepiandosterone sulfate. [a], $P < 0.05$; [b], $P < 0.01$; [c], $P < 0.001$ for the overall effect of a given sex hormone on variables that are related to or part of the metabolic syndrome (ANCOVA). [d], $P < 0.05$; [e], $P < 0.01$; [f], $P < 0.001$ for the linear trend of a given sex hormone as a continuous variable (linear regression). Units for the variables in the top row as in Table 1.

## Discussion

This is one of the few studies in a large population-based cohort showing that non-diabetic men with mild hypoandrogenism are more likely to have a concurrence of risk factors related to the metabolic syndrome than men with higher testosterone levels, even after adjusting for BMI and potential confounding factors, and to our knowledge it is the first to demonstrate an association with the metabolic syndrome using a standard definition. Moreover, low concentrations of total and free testosterone and SHBG were consistently associated with components of and features related to the metabolic syndrome, including inflammation and measures of iron status.

Men with total testosterone levels in the lower third were over 3.5-fold more likely to have the metabolic syndrome than men with concentrations in the upper third, and were nearly two times more likely to have the metabolic syndrome even after adjusting for BMI. Moreover, men with free testosterone levels in the lower third were still 1.7–2.8 times more likely to have the metabolic syndrome after excluding men with cardiovascular disease. Use of the NCEP definition of the metabolic syndrome instead or use of clinically applicable dichotomous cut-offs for hypoandrogenism gave qualitatively similar findings. Thus mild hypoandrogenism in men can be considered a feature of the metabolic syndrome even before development of late-stage consequences such as type 2 diabetes or cardiovascular disease.

Supporting the association of hypoandrogenism with the metabolic syndrome, low concentrations of total and free testosterone were consistently associated not only with core components of the metabolic syndrome, but also with measures related to inflammation and iron storage, independently of age and BMI. We are unaware of any previous reports on the association of sex hormones with measures of inflammation or iron storage. The inverse association with CRP may be mediated indirectly through the metabolic syndrome.

CRP-adjusted ferritin, a common measure of iron stores, were elevated in men with low testosterone levels and also in men with the metabolic syndrome. Testosterone levels are decreased in haemachromatosis (31), presumably caused by the toxic effect of excess iron in testicular tissue and the hypophysis itself. The effect of iron in the high normal range on testosterone levels is not known. Even though both high haemoglobin concentrations and low testosterone levels were associated with the metabolic syndrome, men with low-normal free and total testosterone levels also had slightly lower haemoglobin levels even after adjustment for BMI and smoking. Exogenous testosterone is known to increase haemoglobin production independently of iron stores, whereas low testosterone levels are associated with a decrease in haemoglobin (32).

**Table 3** Odds ratios (95% confidence intervals) for having the metabolic syndrome according to categories of sex hormones in 1865 non-diabetic middle-aged men.

| | Model 1[a] | Model 2[b] | Model 3[c] |
|---|---|---|---|
| **Total testosterone** (nmol/l) | | | |
| 23.4–51.7 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 17.0–23.3 | 1.88 (1.33–2.66) | 1.88 (1.33–2.66) | 1.47 (1.02–2.13) |
| 1.1–16.9 | 3.60 (2.62–4.93) | 3.69 (2.66–5.11) | 1.91 (1.34–2.74) |
| *P* for linear trend | <0.001 | <0.001 | 0.002 |
| **Free testosterone** (pmol/l) | | | |
| 332–717 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 266–331 | 1.56 (1.13–2.16) | 1.54 (1.11–2.15) | 1.27 (0.89–1.81) |
| 10–265 | 2.73 (2.01–3.69) | 2.84 (2.08–3.89) | 1.71 (1.21–2.41) |
| *P* for linear trend | <0.001 | <0.001 | 0.008 |
| **SHBG** (nmol/l) | | | |
| 43.8–131.9 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 30.6–43.7 | 1.93 (1.39–2.67) | 2.05 (1.46–2.87) | 1.48 (1.02–2.14) |
| 4.6–30.5 | 3.43 (2.50–4.70) | 3.46 (2.49–4.82) | 1.86 (1.30–2.69) |
| *P* for linear trend | <0.001 | <0.001 | 0.003 |
| **DHEAS** (μmol/l) | | | |
| 4.79–16.0 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 3.11–4.78 | 0.74 (0.55–1.01) | 0.75 (0.55–1.02) | 0.75 (0.53–1.05) |
| 0.80–3.10 | 1.08 (0.80–1.44) | 1.10 (0.82–1.49) | 1.11 (0.79–1.56) |
| *P* for linear trend | 0.57 | 0.59 | 0.62 |

[a], Adjusted for age category; [b], adjusted for age category, smoking (not at all, 1–19 cigarettes per day or 20 or more cigarettes per day), alcohol consumption (abstainers and low, moderate and high intake according to g/week consumption), cardiovascular disease and adulthood socioeconomic status; [c], adjusted for (b) and body mass index.

Low levels of free or total testosterone have consistently been associated with overall or abdominal obesity, insulin resistance or hyperinsulinaemia, hyperglycaemia and dyslipidaemia (8–12). The associations have in some studies persisted even after adjustment for adiposity (9, 11–13). In these men, the association with waist-hip ratio disappeared after adjustment for BMI. Most studies have been too small to reliably determine a residual effect of abdominal obesity as measured by computed tomography or magnetic resonance imaging or as roughly measured by waist or waist-hip ratio after adjustment for measures of overall obesity. Nonetheless, low testosterone levels have predicted an increase in visceral fat during follow up (14). We also found a weak inverse association of total and free testosterone with blood pressure. The Rancho Bernardo study also found an inverse association of testosterone levels with blood pressure in 1132 men (33).

Testosterone itself may have a causal role in the pathogenesis of the metabolic syndrome or its components by increasing muscle mass at the expense of fat mass and decreasing abdominal obesity by inhibiting lipoprotein lipase activity (18). Some studies have found that administration of testosterone or stimulation of testosterone secretion improves insulin sensitivity via a reduction in circulating non-esterified fatty acids (18). Our finding of a strong inverse association of total and free testosterone concentrations with non-esterified free fatty acids is consistent with this hypothesis. Exogenous testosterone may also have a favourable effect on the lipid profile, although HDL levels have sometimes decreased (34). Whether testosterone mediates its effect on blood pressure indirectly through the association of testosterone with the metabolic syndrome or directly through effects on the vascular endothelium is not known (34).

Conversely, overall or abdominal obesity may cause a decrease in free and total testosterone levels in men. The effect of weight loss on free and total testosterone and sex hormone-binding globulin has been inconsistent, but overall or abdominal obesity increases glucocorticoid turnover and production (19, 20), resulting in abnormal control of the hypothalamic–pituitary–adrenal axis and possibly mild hypoandrogenism in men. Furthermore, obesity is associated with abnormally increased expression and activity of the enzyme 11β-hydroxysteroid dehydogenase type 1 (11β-HSD-1) in adipose tissue (35–37). 11β-HSD-1 plays a pivotal role in determining local glucocorticoid concentrations by interconversion of cortisol and its inactive counterpart, cortisone.

Men with low SHBG concentrations were not only several times more likely to have the metabolic syndrome than men with higher levels, but were also consistently more likely to have features associated with the metabolic syndrome. SHBG has previously been shown to be inversely related to components of the metabolic syndrome, and may predict development of diabetes (16, 38). Inhibition of insulin secretion by diazoxide leads to increased SHBG levels (39), suggesting that SHBG production in the liver is regulated by insulin. Mechanisms by which SHBG itself may directly influence development of the metabolic syndrome are unclear, but at the very least

SHBG seems to be a good marker for the metabolic syndrome and the risk for further metabolic decompensation.

DHEAS levels were not associated with insulin levels. A large study in over 700 male French twins also found no association between insulin and DHEAS concentrations (40), in agreement with a small population-based study in older Finnish men in which insulin resistance was measured with a euglycaemic hyperinsulinaemic clamp (10). Some smaller studies have reported inverse associations (11). Men with higher levels of DHEAS had a more favourable lipid profile, but also had higher blood pressure and higher blood glucose concentrations. Higher HDL cholesterol levels in men with high DHEAS concentrations are consistent with findings in 178 men from the San Antonio Heart Study (13). A positive association of DHEAS with blood pressure has also been found previously in a gender-based sub-group analysis in 646 middle-aged men and women participating in a population-based cohort study (41).

The strengths of this study include its large, population-based design and detailed assessment of features that are part of or related to the metabolic syndrome, including inflammation and iron status. The cross-sectional nature of the study design does not, however, allow conclusions to be drawn about causality. We calculated free testosterone levels rather than directly determining bioavailable testosterone levels, but calculation of free testoterone from total testosterone and SHBG has been shown to be accurate in healthy persons and in several pathological conditions (42, 43).

Non-diabetic middle-aged men with low-normal concentrations of total and free testosterone and sex hormone-binding globulin were more likely to have the metabolic syndrome than men with high-normal testosterone levels, independently of body mass index. Consistently, individual core components and other features of the metabolic syndrome, including inflammation and markers of iron storage, were also exaggerated. DHEAS levels, on the other hand, were not associated with the metabolic syndrome, but men with high-normal DHEAS levels had higher blood pressure and higher levels of blood glucose despite having a more favourable lipid profile. Even in the absence of diabetes and cardiovascular disease, subtle derangements in sex hormones are present in the metabolic syndrome, and may contribute to its pathogenesis.

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