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Association of hormonal dysregulation with metabolic syndrome in older women: data from the InCHIANTI study

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Abstract

Metabolic syndrome (MetS) is a strong risk factor for type 2 diabetes and cardiovascular disease. Conditions associated with hyperandrogenism are often associated with glucose intolerance and other features of MetS in young women. As the prevalence of MetS increases with age and is probably multifactorial, it is reasonable to hypothesize that age-related changes in androgens and other hormones might contribute to the development of MetS in older persons. However, this hypothesis has never been tested in older women. We hypothesized that high levels of testosterone, dehydroepiandrosterone sulfate (DHEA-S), and cortisol and low levels of sex hormone-binding globulin (SHBG) and IGF-I would be associated with MetS in a representative cohort of older Italian women independently of confounders (including inflammatory markers). After exclusion of participants on hormone replacement therapy and those with a history of bilateral oophorectomy, 512 women (≥ 65 yr) had complete data on testosterone, cortisol, DHEA-S, SHBG, fasting insulin, total and free IGF-I, IL-6, and C-reactive protein (CRP). MetS was defined according to ATP-III criteria. Insulin resistance was calculated according to HOMA. MetS was found in 145 women (28.3%). Participants with vs. those without MetS had higher age-adjusted levels of bioavailable testosterone ($P < 0.001$), IL-6 ($P < 0.001$), CRP ($P < 0.001$), and HOMA ($P < 0.001$) and lower levels of SHBG ($P < 0.001$). After adjustment for potential confounders, participants with decreased SHBG had an increased risk of MetS ($P < 0.0001$) vs. those with low SHBG. In a further model including all hormones and confounders, log SHBG was the only independent factor associated with MetS (OR: 0.44, 95% CI 0.21–0.91, $P = 0.027$). In older women, SHBG is negatively associated with MetS independently of confounders, including inflammatory markers and insulin resistance. Further studies are needed to support the notion that raising SHBG is a potential therapeutic target for prevention and treatment of MetS.

Keywords

sex hormone-binding globulin; hormonal dysregulation; insulin-like growth factor I; androgens

The national cholesterol education program's Adult Treatment Panel III report (ATP-III) has defined the metabolic syndrome (MetS) as an aggregation of cardiovascular risk factors including low HDL-cholesterol and high fasting glucose, triglycerides, waist circumference, and blood pressure (13,15). MetS is a strong risk factor for cardiovascular disease and type 2 diabetes (32–33). The prevalence of the MetS is 22–24% in the US population (13) and 15–18% in the Italian population (25) and tends to increase with age (13,22,33). Recent data from older American and Italian cohorts suggest that MetS prevalence is higher in women than in men (22,33).

In the elderly, MetS is probably multifactorial (27). In particular, age-associated changes in hormonal levels might contribute to the development of MetS. Higher androgen levels have been linked to MetS or its components in women (26). Moreover, MetS or its individual components are common features in young women with polycystic ovary syndrome (PCOS), characterized by increased levels of androgens and inflammatory markers (10,11). Sex hormone-binding globulin (SHBG), the circulating protein that binds testosterone and estradiol, has low levels in patients with hyperandrogenism (2) and may play a role in the pathogenesis of MetS (16). Furthermore, previous studies have suggested that low insulin-like growth factor I (IGF-I) and high cortisol are significant correlates of MetS (5,31,34,35).

Overall, this literature suggests that hormonal changes that occur as a part of the aging process may predispose to MetS; however, no study has yet addressed the relationship between multiple hormonal dysregulation and MetS in older women. To diminish this gap in the literature, we studied the relationship between different hormones and MetS in a representative cohort of older Italian women. We hypothesized that higher androgens and cortisol and lower levels of SHBG and IGF-I would be associated with MetS independently of inflammatory state and other potential confounders.

METHODS

Study population

The Aging in the CHIANTI Area, Invecchiare (InCHIANTI) study is an epidemiological study of a representative sample of the population living in Tuscany, Italy. We selected from this population 592 women 65 yr and older (age range 65–102 yr) who had complete data on testosterone, cortisol, dehydroepiandrosterone sulfate (DHEA-S), IGF-I, SHBG, fasting insulin, C-reactive protein (CRP), interleukin-6 (IL-6), and albumin. We excluded 17 participants who were taking hormone replacement therapy and 63 with a history of oophorectomy. The final analyses were performed in 512 women. The Italian National Institute of Research and Care of Aging Institutional Review Board ratified the study protocol (12).

Definition of MetS

In accordance with the National Cholesterol Education Program's ATP-III criteria, the diagnosis of MetS was established as the presence of three or more of the following features: 1) fasting blood glucose levels ≥ 126 mg/dl or use of hypoglycemic medications, 2) fasting serum triglycerides ≥ 150 mg/dl or use of hypolipemic medications, 3) serum HDL < 50 mg/dl, 4) blood pressure $\geq 130/85$ mmHg or use of antihypertensive medications, and 5) waist circumference > 88 cm (39).

Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest (normally umbilical level). Weight and height were measured using standard techniques. Body mass index (BMI) was calculated as weight divided by height (kg/m^2). Baseline blood pressure was recorded using a standard mercury sphygmomanometer. All blood pressure measurements were performed with the participant in a supine position on three occasions separated by intervals of 2 min, and the average of the last two measurements was used in the analysis. History of hypertension or use of antihypertensive medications was considered to define hypertension.

Hormone assays

Fasting blood samples were drawn between 7:00 and 8:00 AM and were stored at -80°C until analysis. Cortisol, DHEA-S, total testosterone, and total IGF-I were assayed using commercial kits (Diagnostic Systems Laboratories, Webster, TX). For cortisol, the minimum detection limit was $0.5 \mu\text{g}/\text{dl}$; intra-assay and interassay coefficients of variation (CVs) were $<10\%$. For DHEA-S, the minimum detection limit was $1.7 \mu\text{g}/\text{dl}$; intra- and interassay CVs for three different concentrations ranged between 4.1 and 5.3% and between 4.6 and 7.0%, respectively. For total testosterone, the minimum detection limit was $0.03 \text{ nmol}/\text{l}$; intra- and interassay CVs for three different concentrations were <9.6 and 9.1% , respectively. Total IGF-I was measured by IRMA. Inter- and intra-assay CVs for three concentrations (low, medium, high) were all $<10\%$. Free IGF-I was measured by commercial radioimmunoassay (Diagnostic System Laboratories) Inter- and intra-assay CVs were 6.2 and 7.3%, respectively.

SHBG was measured by a radioimmunoassay (Diagnostic Products, Los Angeles, CA) with a minimum detected concentration of $0.04 \text{ nmol}/\text{l}$ and inter- and intra-assay CVs for three concentrations <6.9 and 3.6% , respectively (36).

Concentration of bioavailable testosterone was calculated using the Vermeulen formula (23, 37). Plasma insulin level was determined with a double-antibody, solid-phase radioimmunoassay (intra-assay CV = $3.1 + 0.3\%$; Sorin Biomedica, Milan, Italy). Cross-reactivity with human proinsulin was 0.3% (1).

Serum glucose level was determined by using an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) and a Roche-Hitachi 917 analyzer. Insulin resistance (IR) was calculated according to homeostasis model assessment (HOMA): $\text{IR} = \text{fasting insulin} \times \text{fasting glucose}/22.5$ (6,24).

Inflammatory markers

Serum IL-6 was measured by high-sensitivity ELISA (BIOSOURCE, Camarillo, CA). The lowest detectable concentration was $0.1 \text{ pg}/\text{ml}$, with an interassay CV of 7% . High-sensitivity CRP was measured in duplicate by enzyme-linked immunosorbent assay using purified protein and polyclonal CRP antibodies (Calbiochem, San Diego, CA) with standardization according to the World Health Organization's reference standard. The minimum detectable concentration was $0.03 \text{ mg}/\text{l}$, and the interassay CV was 5% .

Plasma HDL-cholesterol and triglyceride concentrations were assessed using commercial kits (Roche Diagnostics, Mannheim, Germany). The interassay CV was $<3.8\%$ for HDL-cholesterol and $<2.5\%$ for triglycerides.

Assessment of covariates

Glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels were determined using commercial kits (Roche Diagnostics). The measurement unit was expressed as units per liter, the analytic sensitivity was $4 \text{ U}/\text{l}$ for both tests, and the intra- and

interassay CVs were <2.0 and 4.0% for GOT and GPT, respectively. Serum albumin was measured with agarose electrophoretic technique [Hydragel Protein (E) 15/30; Sebia, Issy-les-Moulineaux, France] and was expressed in percent.

Physical activity during the year prior to the interview was coded as 1) sedentary: completely inactive or light-intensity activity <1 h/wk; 2) light physical activity: light-intensity activity 2–4 h/wk; 3) moderate-high physical activity: light activity ≥ 5 h/wk or more or moderate activity ≥ 1 –2 h/wk. Daily alcohol (g) intake was estimated by the European Prospective Investigation Into Cancer and Nutrition Food Frequency Questionnaire (28). Smoking was assessed by self-report and expressed as pack-years (packs smoked per day $\times$ years of smoking). Sociodemographic variables included age, sex and educational level.

Statistical analysis

Because of skewed distributions, log-transformed values for SHBG, CRP, IL-6, DHEA-S, bioavailable testosterone, and insulin were used in the analyses. Differences in hormonal levels and other parameters among participants with and without MetS were tested by age-adjusted ANCOVA. SHBG levels were divided into quartiles to better describe their relationship with MetS. Differences in the prevalence of MetS according to specific hormone quartiles were formally tested by Pearson χ^2 tests.

Odds ratios (ORs) of having MetS associated with hormonal levels adjusted for confounders (age, smoking, alcohol consumption, physical activity in the year before the visit, log CRP, log IL-6, HOMA, GOT, GPT, albumin) were estimated from logistic regression models. A multiple logistic regression analysis with all hormones was used to assess the association between each hormone and the presence of MetS. The SAS 8.2 statistical package (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Mean age of the sample was 76 (range 65–102) yr. Table 1 shows the general characteristics of the study population according to the presence or absence of MetS criteria. Overall, 145 women (28.3%) had MetS. As expected, the presence of MetS was associated with lower HDL-cholesterol, albumin, and higher triglycerides, blood glucose, waist circumference, and prevalence of hypertension. Subjects with MetS had higher fasting insulin, IR, bioavailable testosterone, GPT, CRP, and IL-6 levels. Participants with MetS also had lower SHBG (Table 2). No significant association with MetS was found for cortisol, total or bioavailable testosterone, and total IGF-I, whereas the relationship was almost significant for free IGF-I and DHEA-S (Table 3).

After adjustment for multiple confounders, including age, smoking, alcohol consumption, physical activity, log CRP, log IL-6, HOMA, GOT, GPT, and albumin, participants with decreased log SHBG had 60% increased risk ($P < 0.0001$) of having MetS (Table 3). After further adjustment for all other hormones, the relationship between log SHBG and MetS did not change (OR: 0.44, 95% CI 0.21–0.91, $P = 0.027$). In this model, participants' log free IGF-I was also independently associated with MetS (OR: 0.61, 95% CI 0.37–1.01, $P = 0.05$). No significant association was found between MetS and other hormones (Table 4).

Figure 1 shows the number and percentage of participants with and without MetS according to the quartiles of SHBG. The percentage of participants with MetS was significantly lower among participants in the higher quartiles of SHBG (age-adjusted P for trend <0.001).

In age-adjusted analyses, log SHBG was positively associated with HDL ($P < 0.001$) and negatively associated with triglycerides ($P < 0.001$), waist circumference ($P = 0.01$), and

glucose ($P = 0.006$) and almost significantly associated with blood pressure ($P = 0.06$). Even after adjustment for age, smoking, alcohol intake, and physical activity in the year before the visit, log IL-6, log CRP, GOT, GPT, albumin, and HOMA, log SHBG was positively associated with HDL ($P = 0.02$) and negatively associated with triglycerides ($P < 0.001$) but not with blood pressure, glucose, and waist circumference. Log free IGF-I was negatively associated with waist circumference ($P = 0.01$) but not with other components of MetS. In the fully adjusted analysis, log free IGF-I was negatively associated with glucose levels ($P = 0.02$) but not with other components of MetS. No significant independent association was found between log cortisol, log DHEA-S, total testosterone, and log bioavailable testosterone, log total IGF-I, and the individual components of MetS in the fully adjusted analyses.

DISCUSSION

In this older female population, the prevalence of MetS was 28.3%, which is comparable to the rates previously reported from US and Italian populations using the same classification criteria of MetS (13,32,33). In a representative sample of older Italian women, we found a negative relationship between SHBG and MetS independent of potential confounders, and after adjustment for the effect of other hormones. To our knowledge, this is the first study that has tested the association between hormonal dysregulation and MetS in a population of older women.

The most intriguing finding was the strong negative relationship of SHBG with MetS and its components, namely HDL-cholesterol and triglycerides. This is the first evidence of an independent association between SHBG and MetS in an older female population, as previous studies were restricted to premenopausal or younger postmenopausal women (11,16,26).

Our findings are in contrast with those reported by Hajamor et al. (16), who failed to detect a significant correlation between SHBG and MetS in postmenopausal women. However, the limited number of subjects ($n = 46$) and the younger age of participants with MetS in that study may account for the different results. It is known that SHBG concentrations are tightly regulated by sex hormones. In women, SHBG concentrations are increased by estradiol (which has higher affinity than testosterone for SHBG) and decreased by testosterone. Thus low SHBG levels per se are considered an indirect index of androgenicity (2). It has also been demonstrated that SHBG concentration is influenced by insulin levels; both in vitro studies in human hepatoma cell lines (Hep G2) and in vivo observations, for example during hyperinsulinemic euglycemic clamp, provide evidence for this notion (20,29). However, even when HOMA (which reflects insulin levels) and the effect of different hormones were considered in the analysis with other potential confounders, the relationship between SHBG and MetS was still significant.

These findings confirm a recent meta-analysis suggesting that SHBG predicts the development of MetS and type 2 diabetes independently of fasting insulin levels (8).

Interestingly, in our study, participants with MetS had higher GPT and lower albumin levels, suggesting the existence in MetS of a liver dysfunction that potentially affects SHBG synthesis (17). However, after adjustment for liver function (GOT, GPT, and albumin), the strength of the association between SHBG and MetS was not affected.

Although our study does not provide clues for the mechanisms of this effect of SHBG on MetS, it is interesting to speculate that SHBG may be much more than a mere transport protein. Despite failures to clone a specific SHBG membrane receptor, signaling for SHBG has been detected in different tissues including prostate, testis, breast, liver, and possibly muscles (18–19). It has also been suggested that SHBG may reflect the integration of several hormonal and nutritional stimuli (16). Of note, in our study, SHBG levels were negatively and independently associated with low HDL ($P < 0.05$) and triglycerides ($P < 0.001$), suggesting that SHBG might

have a regulatory effect on hepatic lipase activity (30). Our results are concordant with those reported by Mudali et al. (26) and Bataille et al. (4) in postmenopausal women of younger age.

Low IGF-I levels have been associated with some features of MetS and insulin resistance and have been shown as an independent predictor of incident diabetes (1,34–35). In our study, we found no significant difference in free and total IGF-I levels between participants with and without MetS. However, in the multivariate analysis, free IGF-I (the biologically active fraction of IGF-I), but not total IGF-I, levels were almost significantly associated with MetS, partially confirming what Sesti et al. (34) found in a younger population using different criteria of MetS (World Health Organization criteria). The discrepancy between the age adjusted and the multivariate analyses provides ground for the hypothesis that the hormonal dysregulation rather than alteration of one single hormone is associated with MetS.

In accord with previous literature, we found that total and bioavailable testosterone were higher in women with MetS (7,21,26). However, after adjustment for potential confounders, the strength of this association was substantially weakened and was no longer statistically significant. The lack of association between bioavailable testosterone and MetS in the multivariate analysis is not surprising, since the analysis was adjusted for HOMA and inflammatory markers, factors that may impact testosterone concentration (11).

Although the causality of the relationship between inflammation and hyperandrogenism is still uncertain, recent studies in subjects with PCOS suggest that hyperandrogenism is the consequence of the activation of nuclear factor- κ B and the subsequent inflammatory cascade (14). Our data support this hypothesis in the older population.

In fact, when we incorporated IL-6 and CRP in the multivariate analysis, the relationship between bioavailable testosterone and MetS was no longer statistically significant. To test the association between testosterone and MetS in older women, we excluded those with history of oophorectomy (because ovaries are an important source of testosterone in postmenopausal women) and those who were on hormone replacement therapy (because estradiol raises SHBG and reduces free androgens). Hence, the comparability between our study and other reports in the literature that focused on younger women is limited (21,26).

We did not find any significant difference in serum DHEA-S levels between participants with and without MetS in either univariate or multiple logistic analyses. Although there is growing evidence of a protective role for DHEA in MetS in men, the role of DHEA-S in women is controversial (3,38). Barrett-Connor et al. (3) showed a positive association between DHEA-S and single components of MetS, namely waist circumference and glucose tolerance. In contrast, Villareal et al. (38) reported an improvement in insulin sensitivity after DHEA treatment. We also found no differences in cortisol between subjects with and without the MetS. However, serum cortisol levels do not necessarily reflect tissue cortisol (especially abdominal adipose tissue) (9). More importantly, we only measured serum cortisol levels measured at 8 AM and not the 24-h urine levels of free cortisol. This limited our capability of laying out the association between cortisol and MetS.

The main limitation of our study is its cross-sectional design. Given the nature of the study, we cannot establish whether altered hormonal levels are a cause or consequence of MetS. Second, we did not measure estradiol, and, rather than obtaining a direct measure of bioavailable testosterone, we used estimated levels using a well-accepted formula. Third, information on IGF-I-binding proteins was not available, which might have provided more detail on the biological activity of IGF-I. Finally, in this study, we had only serum cortisol levels measured at 8 AM, which reflect neither 24-h nor adipose tissue levels. However, these limitations are offset by important strengths. This is the first large representative sample of older women with complete information on hormones and ATP-III criteria for MetS who were

screened for multiple potential confounders, such as inflammatory markers, insulin resistance, smoking, physical activity, and alcohol intake. By performing a multivariate analysis including all the hormones, we were able to test for the first time in older women the impact of the hormonal dysregulation rather than a single hormone on MetS. In addition, by excluding participants with a history of oophorectomy and those on hormone replacement therapy, we removed the interferences that may be attributed to these conditions.

In conclusion, our data suggest that SHBG is inversely associated with MetS in older women independently of inflammatory markers, insulin resistance, and other confounders. Further studies are needed to clarify whether SHBG represents a simple marker of hormonal dysregulation or possibly a therapeutic target for MetS (5,10,18,19).

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Fig. 1.

Sex hormone-binding globulin (SHBG) and metabolic syndrome. Percent Distribution of the participants (vertical axis) with metabolic syndrome (bars) according to quartiles (Q1–Q4) of SHBG (horizontal axis). Nos. of participants according to the quartiles of SHBG are indicated in parentheses on the horizontal axis. *P* for trend is age adjusted.

Table 1

Characteristics of general population according to presence of metabolic syndrome in older women

	Criteria for MetS		<i>P</i> Value*
	<3	≥3	
<i>n</i>	367	145	
Age, yr	76.1±7.5	77.0±8.0	0.22
Body mass index, kg/m ²	26.6±4.0	30.3±4.8	<0.0001
HDL-cholesterol, mg/dl	47.3±10.7	64.1±15.1	<0.0001
Tryglicerides, mg/dl	104.8±38.4	178.8±18.5	<0.0001
Blood glucose, mg/dl	88.5±17.4	108.2±34.4	<0.0001
Waist circumference >88 cm, <i>n</i> (%)	124 (85.5)	138 (47.6)	<0.0001
Blood pressure >130/85 mmHg, <i>n</i> (%)	129 (88.0)	207 (56.0)	<0.0001
GOT, U/l median (IQR#)	20.5 (7.1)	20.4 (8.9)	0.82
GPT, U/l, median (IQR#)	17.1 (9.6)	20.9 (15.3)	0.002
Albumin, g/dl, median (IQR#)	58.1 (3.5)	57.6 (3.5)	0.06
CRP, µg/ml, median (IQR#)	3.2 (5.3)	2.4 (4.1)	0.003
Il-6, pg/ml, median (IQR#)	<1.3 (1.2)	1.9 (1.8)	<0.0001
Insulin, mIU/l, median (IQR#)	9.5 (6.3)	11.3 (8.3)	<0.001
HOMA index, median (IQR#)	2.1 (1.4)	2.9 (2.8)	<0.0001
Physical activity last year, h/wk	1.7±0.5	1.7±0.5	0.28
Smoking, packs/yr	2.2±7.4	3.7±11.9	0.09
Alcohol, g/day	8.7±6.6	9.5±7.1	0.33
Formal education, yr	4.6±2.7	4.4±2.7	0.49

Values are expressed as means ± SD unless otherwise indicated. IQR#, interquartile range; HOMA, homeostasis model assessment; GOT, glutamic oxaloacetic transaminase; glutamic pyruvate transaminase; CRP, C-reactive protein.

* Differences in parameters among patients with and without metabolic syndrome (MetS) were tested using age-adjusted ANCOVA.

Table 2

Hormonal parameters according to presence of metabolic syndrome in older women

	Criteria for MetS		<i>P</i> Value [*]
	<3	≥3	
<i>n</i>	367	145	
Total testosterone, ng/dl	60.0 (36.0)	65.0 (42.0)	0.20
Bioavailable testosterone, ng/dl	8.4 (8.8)	12.5 (12.5)	0.004
SHBG, nmol/l	131.2 (90.3)	97.5 (69.7)	<0.0001
DHEA-S, µg/dl	64.5 (76.8)	62.2 (74.8)	0.93
Cortisol, µg/dl	12.9 (5.6)	12.6 (5.4)	0.74
Total IGF-I, ng/ml	97.8 (66.6)	101.1 (75.9)	0.91
Free IGF-I, pg/ml	0.6 (0.3)	0.5 (0.3)	0.29

Values are expressed as medians and IQR unless indicated otherwise. SHBG, sex hormone-binding globulin; DHEA-S, dehydroepiandrosterone sulfate.

* Differences in parameters among patients with and without MetS were tested using age-adjusted ANCOVA.

Table 3

Logistic regression models evaluating the relationship between MetS and circulating levels of hormones in older women

Variable	OR [95% CI]	P Value
Total testosterone	0.78 [0.37–1.64]	0.51
Log bioavailable testosterone	1.01 [0.80–1.39]	0.73
Log SHBG	0.41 [0.27–0.63]	<.0001
Log cortisol	0.59 [0.30–1.17]	0.13
Log DHEA-S	0.78 [0.60–1.01]	0.05
Log free IGF-I	0.65 [0.41–1.03]	0.06
Log total IGF-I	1.01 [0.70–1.46]	0.96

OR, odds ratio; CI, confidence interval. Adjusted for age, smoking, alcohol, and physical activity in the year before the visit, log IL-6, log CRP, GOT, GPT, albumin, and HOMA. Each line reports the result of a separate, fully adjusted model.

Table 4

Logistic regression model evaluating relationship between MetS and circulating levels of different hormones in older women

Variable	OR [95% CI]	P Value
Log bioavailable testosterone	0.96 [0.57–1.63]	0.88
Log SHBG	0.44 [0.21–0.91]	0.027
Log cortisol	0.60 [0.26–1.39]	0.23
Log DHEA-S	0.82 [0.59–1.15]	0.25
Log free IGF-I	0.61 [0.37–1.01]	0.05
Log CRP	1.21 [0.89–1.65]	0.22
Log IL-6	1.53 [1.01–2.34]	0.04
HOMA	5.31 [3.01–9.37]	<0.0001

Adjusted for age, smoking, alcohol, GOT, GPT, albumin, and physical activity in the year before the visit. All parameters reported are inserted together in a fully adjusted model.