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Androgens, Estrogens, and Sex Hormone-Binding Globulin in Middle-Aged Men*

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ABSTRACT. Although the administration of estrogens and androgens can affect the concentrations of sex hormone-binding globulin (SHBG) in men, the relationships between endogenous estrogens and androgens and SHBG are uncertain. Therefore, in a randomly selected cohort of 1640 middle-aged men we measured androgen, estrogen, and SHBG concentrations and obtained the subjects' weight, ethanol intake, and smoking histories. The data were analyzed by stepwise multiple regression, with SHBG as the dependent variable, to compare the role of hormones with that of other factors in the control of SHBG levels. Neither estrone or estradiol nor the testosterone/estradiol ratio was predictive of SHBG levels. However, SHBG concentrations were positively correlated with total testosterone and negatively correlated with percent free and percent albumin-bound testosterone. SHBG concentrations were negatively correlated with estrone sulfate, but were positively correlated with the testosterone/estrone sulfate ratio and the concentrations of free and albumin-bound testosterone. In addition, in all models tested age and body mass index (wt/ht^2), but not smoking or ethanol, were strong predictors of SHBG concentrations. Thus, when present in physiological amounts in the blood as a result of glandular secretion, there is a positive relationship between SHBG concentrations and testosterone and, to a lesser extent, free- and albumin-bound testosterone, but age and body mass index appear to be more important in predicting the SHBG concentration. (*J Clin Endocrinol Metab* **71**: 1442–1446, 1990)

ALTHOUGH the plasma concentration of sex hormone-binding globulin (SHBG) in men can be increased by the administration of estrogens, and decreased by the administration of androgens (1, 2), the role of endogenous hormones in mediating the plasma concentration of SHBG remains uncertain. Studies have reported a correlation between SHBG and lipoprotein levels in men (3) and between estrogens and lipoproteins (4, 5), but the association between SHBG and estrogens has largely been neglected. Women have higher levels of SHBG than men (6), and while the marked shift in estrogen levels through the menstrual cycle have been associated with changes in SHBG levels in some studies (7), other studies have not found these changes (8). The peak concentrations and variability in estrogen levels in cycling women are also greater than those in normal men. Obese men have lower levels of SHBG (9, 10), but higher levels of estrogens (11), than men of normal body weight or body mass index (BMI; wt/ht^2). However, the relationships in obese men among estrogens, androgens, and SHBG are not well established.

To explore these relationships, we measured estrogens, androgens, and SHBG in a large cohort of men, and now report the results of the analysis of these data.

Materials and Methods

The study population consists of randomly selected middle-aged men (38–70 yr old) from the greater Boston, MA, area. A two-stage self-weighted cluster sampling scheme was used. First, 11 cities and towns from the Boston Standard Metropolitan Statistical Area were randomly selected, using probabilities proportional to population size, within 6 strata defined by income and town/city size. Second, men born between 1917 and 1946 were randomly selected from the city or town street lists (updated annually), using sampling fractions adjusted to yield a uniform age distribution.

An introductory letter was sent to each selected individual, followed up by a telephone call to elicit participation and schedule the interview. The final response rate was 53%, ranging from 48% in the large cities with average incomes below the state median to 69% in the smaller, more affluent suburbs. A follow-up study of refusers revealed that they were slightly older, had less education, and were less likely to be employed than the original respondents. However, there were no significant differences in the prevalence of chronic diseases between the responders and refusers. In-home interviews were conducted between January 1987 and February 1989. All interviews were scheduled to begin within 2 h of the respondent's usual wake-up time. The interviews covered current medication use

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alcohol intake (12), physical activity (13), and sociodemographic variables. Height and weight were measured directly using standardized techniques described previously (14). Quetelet's BMI, which is weight (kilograms) divided by height (square meters), was also calculated.

Two nonfasting blood samples were drawn 0.5 h apart and within 4 h of awakening. The samples were centrifuged, and the serum was stored at −70 C until analyzed. Equal aliquots from the two samples were pooled for the analysis. Estrone (15), estradiol (15), estrone sulfate (16), testosterone (17), free (18, 19) and albumin-bound testosterone (20, 21), dihydrotestosterone (DHT) (17), and SHBG (kits purchased from Diagnostic Products Corp., Los Angeles CA) were measured using the referenced techniques. The interassay coefficients of variation were less than 13%, and the intraassay coefficients of variation were less than 8% for all determinations.

A total of 1709 men were interviewed. Sixty-nine subjects were excluded from this analysis because they reported use of medications known to affect serum hormone levels or were missing key variables. Several subjects had elevated levels of the independent variables, but exclusion of these outliers had no effect on the models or the statistical significance of the results and are included in the results reported here.

Pearson product-moment correlations (r) were calculated to investigate the associations between variables (22). To investigate the role each of the hormones played in the regulation of SHBG levels, a two-stage procedure was employed. First, log SHBG was regressed on each hormone separately. The log transformation was employed to correct for asymmetry in the distribution of SHBG values (23). Then age (years), BMI (kilograms per m^2), alcohol intake (ounces per day), and current cigarette smoking (yes/no) were added to each regression in a stepwise manner until the entrance criteria ($P < 0.15$ on the partial F test) could not be met (24).

A final model was needed to explain the influence of all of the hormones on log SHBG, taking into account the collinearity among the predictors. With log SHBG as the dependent variable, all hormones and covariates were added, again using stepwise regression, until the entry criteria ($P < 0.15$ on the partial F test) could no longer be met. Owing to concerns about the validity of the models obtained by using stepwise procedures, backward elimination was also employed, starting with a model that contained all statistically significant hormones and the four covariates. The same results were obtained. SASpc was used for all statistical analyses (25).

Results

Characteristics of the study population are presented in Table 1. Cigarette smoking status was coded as a dummy variable (1, current cigarette or cigarello smokers; 0, nonsmokers and those using pipes, cigars, or chewing tobacco). The category "Any smoking" refers to users of any or all forms of tobacco products listed above. Thirty percent (n = 178) of those using pipes, cigars, and/or chewing tobacco were also cigarette smokers and were coded as current smokers. Tobacco users who did not smoke cigarettes (n = 124) were coded as nonsmokers, but they accounted for only 7% of the total population and 10% of nonsmokers. These nonsmokers used tobacco products at a much lower frequency than cigarette smokers, with 42% smoking no more than once a day. Table 2 lists the means and SDs of the hormones of interest.

TABLE 1. Characteristics of the men sampled

No.	1640
Age (yr)	54.6 ± 8.7[a]
Wt (kg)	84.5 ± 14.1
BMI (kg/m^2)	27.5 ± 4.4
Cigarette smokers (%)	26
Any smoking (%)	33.1

[a] Mean ± SD.

TABLE 2. Mean serum concentrations of estrogens, androgens, and SHBG

Estrone (pmol/L)	117 ± 59[a]
Estradiol (pmol/L)	110 ± 54
Estrone sulfate (pmol/L)	1173 ± 617
Testosterone (nmol/L)	11.1 ± 5.7
Nonprotein-bound testosterone (nmol/L)	0.21 ± 0.11
Albumin-bound testosterone (nmol/L)	4.01 ± 2.60
DHT (nmol/L)	0.89 ± 0.59
SHBG (nmol/L)	32 ± 16

[a] Mean ± SD.

Log SHBG was negatively correlated with BMI and weight, but was positively correlated with age (r = −0.27, −0.24, and 0.22; $P < 0.001$). SHBG levels were higher in cigarette smokers than in nonsmokers ($t = -2.6$; $P < 0.01$), but cigarette smoking was not a statistically significant covariate when age and BMI were in the regression equation predicting log SHBG. In none of the models tested was ethanol a statistically significant predictor of SHBG concentration, so it is not included in any of the results reported below.

Many of the independent variables and covariates of interest noted above were correlated with each other, and it is important to understand their interrelationships in assessing their contributions to the model. For example, cigarette smokers were thinner (r = −0.08; $P = 0.0126$) and drank more alcohol (r = 0.09; $P < 0.001$) than nonsmokers. Age was inversely correlated with weekly alcohol intake (r = −0.05; $P = 0.0482$) and positively with BMI (r = 0.06; $P = 0.0139$).

Estrone was not a statistically significant predictor of log SHBG in these models. While estradiol was marginally significant, given the large number of models investigated, this may be a spurious result. Estrone sulfate was negatively associated with log SHBG. The estrogen models are presented in Table 3. Estimates of regression coefficients and corresponding SEs are given for each variable. The square of the multiple correlation coefficient (r^2), which is the proportion of total variation in the dependent variable explained by the regression, is

TABLE 3. Linear regressions of log SHBG on each of the three estrogens, controlling for age, BMI, and cigarette smoking

Hormone	Regression coefficient (SE)				Model r^2
	Hormone	Age	BMI	Cigarette smoking	
Estrone	0.0008	0.0124[a]	−0.0291[a]	0.0475	0.13
	(0.0005)	(0.0012)	(0.0025)	(0.0294)	
Estradiol	0.0017[b]	0.0125[a]	−0.0292[a]	0.0482	0.13
	(0.0007)	(0.0012)	(0.0246)	(0.0249)	
Estrone sulfate	−0.0002[a]	0.0122[a]	−0.0275[a]	0.0468	0.14
	(0.00005)	(0.0012)	(0.0025)	(0.0247)	

[a] $P < 0.01$.
[b] $P < 0.05$.

TABLE 4. Linear regressions of log SHBG on each of the four androgens, controlling for age, BMI, and cigarette smoking

Hormone	Regression coefficient (SE)				Model r^2
	Hormone	Age	BMI	Cigarette smoking	
Testosterone	0.0746[a]	0.0134[a]	−0.0237[a]	—[b]	0.20
	(0.0063)	(0.0012)	(0.0024)		
DHT	0.5521[a]	0.0126[a]	−0.0258[a]	—	0.17
	(0.0619)	(0.0012)	(0.0024)		
Free testosterone	−0.2375[a]	0.0094[a]	−0.0247[a]	0.0365	0.20
	(0.0198)	(0.0012)	(0.0024)	(0.0240)	
Albumen-bound testosterone	−0.0074[a]	0.0109[a]	−0.0259[a]	0.0450	0.19
	(0.0007)	(0.0012)	(0.0024)	(0.0242)	

[a] $P < 0.01$.
[b] Not entered into the stepwise model at entry criteria of $P < 0.15$.

also provided for each final regression model.

The testosterone-based hormones were statistically significant predictors of SHBG concentration ($P < 0.001$; see Table 4). SHBG varied directly with testosterone and DHT concentrations and inversely with percentages of albumin-bound and free testosterone. Because the percentages of albumin-bound and free testosterone provided more information than the absolute concentrations of these values (as measured by the partial F statistic), the percentage measures are presented here. The ratios of testosterone to estrogens (estrone, estradiol, and estrone sulfate) were all predictive of log SHBG, with testosterone/estrone sulfate being the strongest predictor (see Table 5). However, in each of the three models, the particular testosterone/estrogen ratio explains a smaller percentage of the variation in log SHBG than testosterone alone, possibly indicating that instead of contributing information to the log SHBG models, the addition of estrogens as a ratio of testosterone dilutes the predictive power of testosterone.

We also noted correlations between the hormones of interest and other independent variables. All estrogens

TABLE 5. Linear regressions of log SHBG on three testosterone/estrogen (T/E) ratios, each controlling for age, BMI, and cigarette smoking

Estrogen in ratio	Regression coefficient (SE)				Model r^2
	T/E ratio	Age	BMI	Cigarette smoking	
Estrone	1.1096[a]	0.0130[a]	−0.0255[a]	0.0566[b]	0.16
	(0.1536)	(0.0012)	(0.0025)	(0.0245)	
Estradiol	0.8189[a]	0.0127[a]	−0.0260[a]	0.0474	0.15
	(0.1356)	(0.0012)	(0.0025)	(0.0247)	
Estrone sulfate	12.1907[a]	0.0124[a]	−0.0244[a]	0.0356	0.18
	(1.2049)	(0.012)	(0.0024)	(0.0242)	

[a] $P < 0.01$.
[b] $P < 0.05$.

and androgens were correlated with BMI ($P < 0.02$); estrone, testosterone, DHT, and percent free testosterone were correlated with cigarette smoking (r = 0.08, 0.09, 0.08, and −0.06; $P < 0.02$); and testosterone and the percent free and albumin-bound testosterone were correlated with age (r = −0.09, −0.12, and −0.19; $P < 0.001$).

Discussion

The cohort we have sampled represents an unselected group of men who were chosen from communities in Massachusetts. These men were between the ages of 38–70 yrs and most were still working. This represents one of the largest cohorts so far reported in studies of the possible relationships between SHBG concentrations and hormones.

Although the oral administration of estrogens has been shown to result in increases in SHBG (1), it has been harder to demonstrate a relationship between SHBG levels and endogenous estrogens in normal men. Our data would indicate that estrone and estradiol concentrations within the physiological range are poor predictors of SHBG concentration and can explain little of the variation in its concentration. The serum concentration of estrone sulfate was negatively correlated with SHBG, which is opposite the effects of estrone sulfate on SHBG when estrogen is administered by mouth (26). Estrone sulfate is formed from estrone (16), probably mainly in the liver, and is not biologically active on its own (27). The weak negative correlation may indicate that a greater diversion of active estrogens to the inactive conjugate estrone sulfate would raise the latter's concentration and result in lower active estrogens and a lessor stimulus of SHBG synthesis.

The increase in SHBG with age has been noted in other reports, and our data confirm these (28–30). Whether this increase is solely an effect of aging or is due to age-related changes in lifestyle is outside the scope of the present report. However, it should also be noted

that not all investigators have found an increase in SHBG with age (31, 32).

The initial studies reporting an inverse correlation between weight or BMI and SHBG involved obese and/or morbidly obese men (9, 10). Although we did not exclude such subjects, the mean weight and BMI of our subjects were well within the ranges for normal men. Thus, the finding in our cohort that weight and BMI were strong predictors of SHBG concentration indicate that these appear to play an important role in determining SHBG levels in normal men. We have also noted such a relationship between SHBG and BMI in normal perimenopausal women (19). The exact mechanism for this relationship in men remains uncertain, but may reflect an action at the hepatic level through either an alteration of synthesis or of glycosylation of SHBG.

Although smoking has been shown to have an effect on androgen levels (33, 34), this alteration appears to be due to a change in body weight and not smoking *per se,* at least in women (35). This indirect relationship would be borne out by our data which showed that BMI was important, but smoking was not, as a predictor of SHBG concentration.

We also found no relationship between alcohol use and SHBG concentrations. Although alcoholic men have higher SHBG levels than nonalcoholics (36), the use of alcohol in the general population does not appear to influence SHBG concentration. We did not specifically compare the SHBG levels in those men who might be considered alcoholic with those in men who were abstainers from alcohol.

The relationship between testosterone and SHBG is a complex one. In situations where SHBG is increased, the percentages of free and albumin-bound testosterone are decreased, but total testosterone is increased (1, 37). The changes in percentage of free testosterone are, thus, considered a function of the change in SHBG. Conversely, in women, when androgens are increased there is an increase in the percentage of free testosterone and a decrease in SHBG, and it has been postulated that the androgen increase results in the decrease in SHBG (38). Our data are in agreement with these results in certain respects, for we found a positive correlation between total testosterone concentration and SHBG and a negative correlation between percentages of free testosterone and SHBG. Both testosterone and percentages of free and albumin-bound testosterone are strong predictors of SHBG concentration, although for percentages of free testosterone and albumin-bound testosterone the correlations are negative, as noted. However, the concentrations of both free testosterone and albumin-bound testosterone are positively correlated with SHBG concentration, but neither of these is a strong predictor of SHBG concentration. We surmise that these weak positive correlations are probably due to the dependence of the concentrations of both free and albumin-bound testosterone on the concentration of total testosterone.

In men, signs of estrogen overactivity, *e.g.* gynecomastia, are often related to a decrease in the testosterone/estrogen ratio rather than an increase in the estrogen concentration *per se* (39). We were unable to find any close relationship between SHBG levels and estrone or estradiol concentrations, while estrone sulfate, an inactive form of estrogen (27), was a strong predictor of SHBG concentration. However, the ratios of testosterone to estrone, estradiol, and estrone sulfate were all found to be relatively strong predictors of SHBG concentrations. The mechanism by which the ratios of testosterone/estrogens become important in predicting SHBG levels is uncertain. Of note is that each of the ratios explained less of the variation in SHBG, as indicated by the squared multiple regression coefficients, than did testosterone alone. The importance of the ratio may simply be a reflection of the concentration of testosterone itself.

Thus, in normal men the control of SHBG concentrations is related not only to the concentrations of androgens and estrogens, but also, and perhaps to a greater degree, to age and weight. The exact mechanism by which age and weight affect SHBG remains uncertain.

References

1. Anderson DC. Sex-hormone binding globulin. Clin Endocrinol (Oxf). 1974;3:69–96.
2. Plymate SR, Leonard JM, Paulsen CA, Fariss BL, Karpas AE. Sex hormone-binding globulin changes with androgen replacement. J Clin Endocrinol Metab. 1983;57:645–8.
3. Haffner SM, Katz MS, Stern MP, Dunn JF. Association of decreased sex hormone binding globulin and cardiovascular risk factors. Arteriosclerosis. 1989;9:136–43.
4. Semmens J, Rouse I, Beilin LJ, Masarei JRL. Relationship of plasma HDL-cholesterol to testosterone, estradiol, and sex-hormone-binding globulin levels in men and women. Metabolism. 1983;32:428–32.
5. Stefanick ML, Williams PT, Krauss RM, Terry RB, Vranizan KM, Wood PD. Relationships of plasma estradiol, testosterone and sex hormone-binding globulin with lipoproteins, apolipoproteins, and high density lipoprotein subfractions in men. J Clin Endocrinol Metab. 1987;64:723–9.
6. Cheng CY, Bardin CW, Musto NA, Gunsalus GL, Cheng SL, Ganguly M. Radioimmunoassay of testosterone-estradiol-binding globulin in humans: a reassessment of normal values. J Clin Endocrinol Metab. 1983;56:68–75.
7. Plymate SR, Moore DE, Cheng CY, Bardin CW, Southworth MB, Levinski MJ. Sex hormone-binding globulin changes during the menstrual cycle. J Clin Endocrinol Metab. 1985;61:993–6.
8. Thijssen JHH. Hormonal and nonhormonal factors affecting sex hormone-binding globulin levels in blood. Ann NY Acad Sci. 1988;538:280–6.
9. Glass AR, Swerdloff RS, Bray GA, Dahms WT, Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J Clin Endocrinol Metab. 1977;45:1211–9.
10. Mello N, Mendelson J, Drieze J, Kelly M. Acute effects of cocaine on prolactin and gonadotropins in female rhesus monkey during the follicular phase of the menstrual cycle. J Pharmacol Exp Ther. 1990;254:815–23.

11. Steger RW, Silverman AY, Johns A, Asch RH. Interactions of cocaine and delta-9-tetrahydrocannabinol with the hypothalamic-hypophysial axis of the female rat. Fertil Steril. 1981;35:567.
12. Khavari KA, Farber PD. A profile instrument for the quantification and assessment of alcohol consumption. J Stud Alcohol. 1978;398:1525–39.
13. Blair SN, Haskell WL, Ho P, et al. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am J Epidemiol. 1985;122:794–804.
14. McKinlay SM, Kipp DM, Johnson P, Downey K, Carleton RA, A field approach for obtaining physiological measures in surveys of general populations: Response rates, reliability, and costs. In: Health Survey Research Methods: Proceedings of the Fourth Conference on Health Survey Research Methods. Washington DC: DHHS; 1984;84–3346.
15. Longcope C, Watson D, Williams KIH. The effects of synthetic estrogens on the metabolic clearance and production rates of estrone and estradiol. Steroids. 1974;24:15–30.
16. Franz C, Watson D, Longcope C. Estrone sulfate and dehydroepiandrosterone sulfate concentrations in normal subjects and men with cirrhosis. Steroids. 1979;34:563–73.
17. Longcope C, Franz C, Morello C, Baker R, Johnston Jr CC. Steroid and gonadotropin levels in women during the peri-menopausal years. Maturitas. 1986;8:189–96.
18. Hammond GI, Nisker JA, Jones LA, Siiteri PK. Estimation of the percent free steroid in undiluted serum by centrifugal ultrafiltration dialysis. J Biol Chem. 1980;255:5023–26.
19. Longcope C, Hui SL, Johnston Jr CC. Free estradiol, free testosterone and sex hormone binding globulin in peri-menopausal women. J Clin Endocrinol Metab. 1987;64:513–8.
20. Hammond GL, Lahteenmaki PLA, Lahteenmaki P, Luukkainen T. Distribution and percentages of non-protein bound contraceptive steroids in human serum. J Steroid Biochem. 1982;17:375–80.
21. Longcope C, Femino A, Johnston JO. Androgen and estrogen dynamics in the female baboon (*Papio anubis*). J Steroid Biochem. 1988;31:195–200.
22. Draper N, Smith H. Applied regression analysis, 2nd ed. New York: Wiley and Sons; 1981;43–7.
23. Snedecor GW, Cochoran WG. Statistical methods, 6th ed. Ames: Iowa State University Press; 1967;141.
24. Draper N, Smith H. Applied regression analysis, 2nd ed. New York: Wiley and Sons; 1981;307–12.
25. SAS/STAT. User's guide, release 6.03 ed. Cary: SAS Institute; 1988.
26. Geola FL, Frumar AM, Tataryn IV, et al. Biological effects of various doses of conjugated equine estrogens in postmenopausal women. J Clin Endocrinol Metab. 1980;51:620–5.
27. Tseng L, Stolee A, Gurpide E. Quantitative studies on the uptake and metabolism of estrogens and progesterone by human endometrium. Endocrinology. 1972;90:390–404.
28. Pirke KM, Doerr P. Age related changes and interrelationships between plasma testosterone, oestradiol and testosterone-binding globulin in normal adult males. Acta Endocrinol (Copenh). 1973;74:792–800.
29. Bartsch W. Interrelationships between sex hormone-binding globulin and testosterone, 5α-dihydrotestosterone and oestradiol-17β in blood of normal men. Maturitas. 1980;2:109–18.
30. Semmens JB, Rouse IL, Beilin LJ, Masarei JRL. Relationships between age, body weight, physical fitness and sex-hormone-binding globulin capacity. Clin Chim Acta. 1983;133:295–300.
31. Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab. 1987;65:1118–26.
32. Kaiser FE, Viosca SP, Morley JE, Mooradian AD, Davis SS, Korenman SG. Impotence and aging: clinical and hormonal factors. J Am Geriatr Soc. 1988;36:511–9.
33. Barrett-Connor E, Khaw K-T. Cigarette smoking and increased endogenous estrogen levels in men. Am J Epidemiol. 1987;126:187–92.
34. Dai WS, Gutai JP, Kuller LH, Cauley JA. Cigarette smoking and serum sex hormones in men. Am J Epidemiol. 1988;128:796–805.
35. Longcope C, Johnston Jr CC. Androgen and estrogen dynamics in pre- and postmenopausal women: a comparison between smokers and nonsmokers. J Clin Endocrinol Metab. 1988;67:379–83.
36. Van Thiel DH, Gavaler JS, Lester R, Loriaux DL, Braunstein GD. Plasma estrone, prolactin, neurophysin, and sex steroid-binding globulin in chronic alcoholic men. Metabolism. 1975;24:1015–9.
37. Siiteri PK, Murai JT, Hammond GL, Nisker JA, Raymoure SJ, Kuhn RW. The serum transport of steroid hormones. Recent Prog Horm Res. 1982;38:457–510.
38. Kirschner MA, Samojlik E, Silber D. A comparison of androgen production and clearance in hirsute and obese women. J Steroid Biochem. 1983;19:607–14.
39. Wilson JD, Aiman J, MacDonald PC. The pathogenesis of gynecomastia. Adv Intern Med. 1980;25:1–32.