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Diet and Sex Hormone-Binding Globulin

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ABSTRACT

The serum concentration of sex hormone-binding globulin (SHBG) is inversely related to weight and in animal studies is inversely related to protein intake. As SHBG can affect the biological activity of testosterone and estradiol, we wished to determine the role of protein intake on SHBG levels in men. Using data from the Massachusetts Male Aging Study we examined cross-sectional relationships between dietary components and SHBG levels in 1552 men (aged 40–70 yr) for whom these factors were known.

Analyzed by multiple regression, controlling for testosterone and estradiol levels, age ($P < 0.001$) and fiber intake ($P = 0.02$) were positively correlated to SHBG concentration, whereas body mass index ($P < 0.001$) and protein intake ($P < 0.03$) were negatively correlated to SHBG concentration. The intakes of calories, fat (animal or vegetable), and carbohydrate were not related to SHBG concentration. We conclude that age and body mass index are major determinants of SHBG concentrations in older men, and fiber and protein intake are also significant contributors to SHBG levels, but total caloric intake and the intake of carbohydrate or fat are not significant. Thus, diets low in protein in elderly men may lead to elevated SHBG levels and decreased testosterone bioactivity. The decrease in bioavailable testosterone can then result in declines in sexual function and muscle and red cell mass, and contribute to the loss of bone density. (*J Clin Endocrinol Metab* **85:** 293–296, 2000)

THE DECLINE in total testosterone levels in men as they age, although not of great magnitude [0.4%/yr for total testosterone (1)], has been consistently demonstrated (2–4) and has been shown to affect a number of factors, including sexual function (5), bone density (6), and atherogenic lipid profiles (7). The decline in total testosterone is accompanied by a decline in the free and bioavailable testosterone (2), and the decline in the latter fractions is amplified by a concomitant increase in sex hormone-binding globulin (SHBG) levels (8); the levels of bioavailable testosterone are inversely related to the levels of SHBG (8). The administration of testosterone (4) has been the major treatment for the decline in bioavailable testosterone, but this treatment may have undesirable side-effects (9). Another approach to increase the bioavailable testosterone would be to decrease the levels of SHBG, which is influenced by a wide range of factors, including age (8), weight (10), and diet (11, 12). Of these factors, the role of diet in SHBG concentrations remains the most uncertain and yet holds great potential for modification.

Several small scale studies of the relation between dietary composition (fiber, caloric, and protein intake) and SHBG levels show conflicting results. In women, a high fiber diet was shown to decrease SHBG levels (13, 14), whereas vegetarians (women and men) were reported to have increased SHBG levels compared to nonvegetarians (14–16). In another study, women with anorexia who were given increased calories had a decrease in SHBG levels (17), whereas other research indicates that a very low calorie diet results in a doubling of SHBG levels over a short term in women with polycystic ovary syndrome (18). Reed *et al.* (12) noted that normal men fed a high fat diet had a decrease in SHBG levels, whereas a diet low in fat resulted in an increase in SHBG levels. Vermuelen *et al.* (19) noted that a high protein diet increased SHBG levels. However, in rabbits fed a diet low in protein, there was a marked increase in SHBG levels (20).

Given these conflicting findings and the potential importance of dietary composition in regulating the circulating concentrations of SHBG (which will, in turn, affect the levels of bioavailable testosterone and estradiol), the purpose of this report was to investigate the relation between dietary components and SHBG with data from the Massachusetts Male Aging Study.

Subjects and Methods

The baseline phase of the Massachusetts Male Aging Study (MMAS), a random sample survey of health and aging in men aged 40–70 yr, was conducted between 1987–1989 in 11 cities and towns in the Boston area (21). Communities were randomly selected, with probabilities proportional to population, within each of 6 strata defined by community size and median income. Men born between 1917–1946 were drawn at random from the annual state census listings. Sampling fractions were adjusted to produce a uniform age distribution between 40–70 yr. Introductory letters were sent to 5287 men, followed by a telephone call encouraging participation. No financial incentive was offered. A total of 1709 respondents (53% of those eligible) enrolled in the study and completed the in-home protocol.

The MMAS participants were typically Caucasian (95%), employed (78%), and married (75%). Nearly half were Catholic (48%). Most had completed high school (71%), and many had earned at least a bachelor's degree (42%). The low representation of racial minorities (4%) was consistent with the composition of the Massachusetts population. The distributions of body mass index (BMI), blood pressure, and serum cholesterol in the MMAS sample closely matched those in the second National Health and Nutrition Examination Survey. The 1563 men who completed the dietary assessment (91.5%) had a slightly higher mean age than those who did not complete it (mean, 55.4 *vs.* 53.2 yr) and a lower prevalence of current cigarette smoking (23.4% *vs.* 35.2%), but did not differ with respect to body weight, BMI, waist/hip ratio (WHR), alcohol intake, or serum concentration of SHBG, testosterone, or estradiol.

Data collection

A trained technician visited each subject in his home between 0800–1000 h and obtained written informed consent. Height, weight, and

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waist and hip circumferences were measured by standardized methods developed for large scale field work (22). Dietary intake was measured by the Willett semiquantitative 1-yr food frequency questionnaire (23). Current cigarette smoking was determined by self report. The subject's customary alcohol intake was estimated by self report of beer, wine, and liquor consumption, accounting for frequency, quantity, and binge drinking, using the Khavari formula (24).

Blood samples were drawn from the antecubital space within 2 h of the subject's awakening to control for diurnal variation. Two tubes were taken 30 min apart for hormone assays and were pooled in equal aliquots at the time of assay to smooth out episodic secretion (25). Blood was kept in an ice-cooled container for transport and was centrifuged within 6 h. Serum was stored in 5-ml scintillation vials at −20 C, shipped to the laboratory on dry ice within 1 week by same-day courier, and stored at −70 C until the time of assay. SHBG was measured by filtration assay (26), with a within-assay coefficient of variation of 8.0% and a between-assay coefficient of variation of 10.9%. Testosterone was measured by RIA (Diagnostic Products, Los Angeles, CA). Estradiol was measured by RIA after solvent extraction and Celite chromatography (27). For both testosterone and estradiol, the inter- and intraassay coefficients of variation were less than 10%.

Data analysis

Serum concentrations of SHBG and estradiol and daily alcohol intake were log transformed for analysis to reduce the influence of extreme values. The resulting distributions were virtually normal as judged by the Shapiro-Wilk statistic ($P > 0.25$).

Pearson correlation coefficients were used to assess the simple association of log SHBG with the following independent variables: age, weight, BMI, WHR, total energy intake (kilocalories per day), serum testosterone and estradiol concentrations, current cigarette smoking, and daily intakes of protein, carbohydrate, fiber, and fat (animal, vegetable, and total).

Multiple regression analysis was conducted to identify a maximal set of independent variables that maintained a statistically significant association with SHBG when controlled for all other variables in the model. An adjusted effect size for each independent variable was constructed from the corresponding log regression coefficient by calculating the percent difference in SHBG resulting from a 1 SD change in the independent variable (in the case of age, a 10-yr change). Statistical Analysis System software was used for all computations (28).

Results

As shown in Table 1, the population was middle-aged and heavy, but not obese (*i.e.* mean BMI <27). Each subject's caloric intake was comparable with his weight, and the dietary make-up reflected a standard western-type diet, with relatively low amounts of fiber.

Simple correlations (Table 2) showed the serum SHBG concentration to be positively associated with age and testosterone level and weakly associated with estradiol level and current cigarette smoking. SHBG was negatively associated with body size, whether measured by weight, BMI (weight for height), or WHR (body habitus). The Pearson correlation was of magnitude 0.2 for each of the anthropometric variables.

Among the dietary variables, SHBG was positively associated with fiber intake and negatively associated with protein and animal fat intake (Table 2). The simple associations with diet and current smoking were weak (Pearson correlation magnitude, 0.05) and marginally significant. Total caloric intake, carbohydrate, alcohol, and vegetable fat showed no association with SHBG. Total fat, the sum of animal and vegetable fat, showed a weak and statistically insignificant association, intermediate in magnitude between those of its two components.

Multiple regression analysis produced a set of 6 variables (Table 3) that were all significantly associated with SHBG when controlled for one another. The model was first identified by a backward elimination procedure, beginning with the 15 variables listed in Table 2. An exhaustive model-testing algorithm confirmed that this model accounted for more variance in SHBG than any other 6-variable model constructed from those 15 predictors. Deletion of 8 outliers (extremely low testosterone, high body size, or high fiber intake) did not affect the selection of variables or parameter estimates. Although no additional variables significantly improved the model, log estradiol was added as a seventh variable because it improved the C_p goodness of fit statistic (29) and because the effect estimates for other variables were thereby adjusted for both major sex steroids. The fraction of variance explained by the 7-variable model was $r^2 = 25\%$.

As in simple correlation analysis (Table 2), age and testosterone level were most strongly associated with SHBG. Body weight, which by itself had a strong correlation with SHBG (Table 2), had no significant independent predictive

TABLE 1. Characteristics of Massachusetts Male Aging Study sample (n = 1563) used in analysis of sex hormone-binding globulin, anthropometrics, and dietary components

Variable	Median	Mean	SD
SHBG (nmol/L)	28.0	32.4	16.5
Testosterone (ng/mL)	5.0	5.2	1.8
Estradiol (pg/mL)	27.0	29.7	14.6
Age (yr)	56.0	55.4	8.6
Wt (lb)	182.0	185.6	31.5
Body mass index (kg/m^2)	26.8	27.4	4.4
Waist/hip ratio (%)	94.5	94.6	6.1
Total energy (Cal/day)	1979	2080	797
Protein (g/day)	76.7	80.0	30.2
Carbohydrate (g/day)	238.3	255.7	111.9
Total fat (g/day)	67.4	72.7	33.4
Animal fat (g/day)	36.6	40.5	21.3
Vegetable fat (g/day)	28.9	32.2	17.9
Fiber (g/day)	18.8	20.4	10.2
Ethanol (oz/day)	0.41	0.80	1.04
Cigarette smoking (%)	—	23.4	—

TABLE 2. Simple correlation of log serum SHBG concentration with anthropometric variables and daily dietary intake: cross-sectional data from Massachusetts Male Aging Study

Variable	Correlation (r)[a]	$P\|H_0:r = 0$
Testosterone	0.36	<0.001
Log estradiol	0.05	0.03
Age	0.20	<0.001
Wt	−0.25	<0.001
Body mass index	−0.26	<0.001
Waist/hip ratio	−0.22	<0.001
Total energy	−0.02	0.38
Protein	−0.05	0.05
Carbohydrate	0.01	0.64
Total fat	−0.04	0.11
Animal fat	−0.05	0.05
Vegetable fat	−0.02	0.50
Fiber	0.05	0.05
Log ethanol	−0.04	0.10
Cigarette smoking	0.06	0.02

[a] Pearson correlation between log SHBG and indicated variable, unadjusted.

TABLE 3. Association of serum SHBG concentration with anthropometric variables and dietary intake: multiple regression analysis of cross-sectional data from Massachusetts Male Aging Study

Independent variable	Unit	Effect size, 95% onfidence interval (%)[a]	$P\|H_0$:no effect
Age	10 yr	14.9 (12.2, 17.7)	<0.001
Serum testosterone	1 SD	16.6 (14.2, 19.1)	<0.001
Log serum estradiol	1 SD	1.4 (−0.7, 3.5)	0.19
Body mass index	1 SD	−5.7 (−7.9, −3.5)	<0.001
Waist/hip ratio	1 SD	−7.1 (−9.2, −4.9)	<0.001
Protein intake	1 SD	−2.8 (−5.3, −0.3)	0.03
Fiber intake	1 SD	3.1 (0.5, 5.8)	0.02

[a] Percent change in serum SHBG associated cross-sectionally with indicated unit change in independent variable, holding all other variables constant.

ability when controlled for BMI and WHR and was not included in the final model. Conversely, both BMI and WHR were significant when controlled for body weight and for each other and were both included in the model.

Protein and fiber, both of which showed weak associations in simple correlation analysis, entered the multiple regression model with slight gains in statistical significance ($P = 0.03$ and $P = 0.02$, respectively). None of the three fat variables (animal, vegetable, and total) was associated with SHBG in multiple regression, whether entered singly or in pairs. Cigarette smoking became insignificant, and total energy, carbohydrate, and alcohol remained insignificant when controlled for other variables. Subjects were questioned as to recent loss of appetite, and men who gave a positive answer to that question did have a slightly higher mean SHBG concentration (36.6 *vs.* 32.0 nmol/L; $P = 0.05$). However, when the appetite variable was added to the multiple regression model the significance greatly diminished ($P = 0.12$), indicating that its effect was explained by the other variables in the model.

To compare effect sizes among the predictors, we used the fitted regression coefficients to calculate the percent change in SHBG corresponding to a 1 SD change in each significant independent variable (Table 3; for age, we used a 10-yr change). Testosterone and age were strongest in effect size as well as statistical significance, producing changes on the order of 15% in SHBG for a 1 SD change in the predictor. The anthropometric variables (BMI and WHR) showed about half that effect (6–7%). The dietary effects were, in turn, half as large (3%).

Discussion

The MMAS comprises a random sampling of men aged 40–70 yr in the Boston, MA, area. It is thus a good representation of that particular area and is representative of men between the ages of 40–70 yr. The data used in this study allowed us to address a number of shortcomings of previous studies, suggesting a link between dietary composition and SHBG. First, it is important to account for other factors that are associated with diet and SHBG, such as age, anthropometrics, and testosterone levels. Many earlier studies of the relation of dietary components to SHBG levels did not consider these factors. By using the broad spectrum of data in the MMAS, we were able to control for demographic, anthropometric, and hormonal factors, all of which could confound any association between diet and SHBG. Second, with the large, randomly selected sample of men who participated in the MMAS, the findings presented can be extrapolated to a broader population than those in other studies based on samples of convenience. Furthermore, the size of the MMAS database allowed us to conduct subgroup analyses that have not been possible in several other small scale studies.

The concentration of SHBG was significantly correlated with age and anthropometrics. These results confirm the findings of others (30, 31). However, we found that weight, which is often used as a predictor of SHBG concentration (10), was not an independent predictor of SHBG when controlled for BMI and WHR. Future investigations should consider measuring BMI and WHR rather than (or in addition to) weight.

The dietary components that correlated best with SHBG levels were protein and fiber. Protein intake, which is marginally significant when tested by simple correlation, is more strongly significant when tested using multiple regression. Thus, the lower the protein intake, the higher the concentration of SHBG. This mirrors our findings in rabbits (20) and indicates that protein intake can be an important control of SHBG level.

The mechanism by which protein intake can be a controlling factor on SHBG concentration is uncertain. One of the major controlling factors on SHBG synthesis is insulin. This intake of protein has been shown to increase insulin levels (32), and insulin has been shown to reduce SHBG levels (33, 34). The effect of protein on SHBG could be mediated in part by its effect on insulin, with a low protein intake leading to low insulin levels and release of the inhibition of SHBG synthesis. If this were to be the mechanism by which protein effects SHBG levels, one would expect that carbohydrate (CHO) intake, a stimulus for insulin release, would also effect SHBG levels. However, we could find no significant relationship between CHO intake and SHBG levels when tested by simple correlation or controlling for other factors. Therefore, it is likely that the relationship of protein intake to SHBG levels involves more than a possible effect on insulin, but it is unclear from our data what that may be. It should be noted that low protein intake was directly correlated with CHO, fat, and caloric intake, so that the lower intake of protein was not being replaced by increased CHO or fat.

It has been suggested that fat intake may be related to SHBG levels (35, 36). In this sample the simple correlation between animal fat and SHBG is significant. However, when controlled for potential confounders such as age, hormones, and anthropometrics, the association no longer remains.

There is conflicting evidence on the importance of fiber intake to SHBG levels. Our finding that fiber intake is correlated positively to SHBG levels, even after controlling for age, testosterone and estradiol, BMI, WHR, and protein intake is at variance with an earlier report indicating a negative correlation between fiber and SHBG. However, other research indicates that increasing fiber intake is associated with higher SHBG. Why our present results are at variance with those of Dorgan *et al.* (37) is not clear, but in that study the caloric intake was almost twice that in the present study, and the study design and analysis

were different from those of the present study and those of the study by Adlercreutz *et al.* (38).

The results of this study have implications for research and clinical practice. In future research of diet and SHBG, the examination of relations between diet and SHBG levels should control for the potential confounding effects of numerous factors, such as age, hormone profiles, and anthropometrics. With regard to practice, in our previous work (39) an increase in SHBG and a related decrease in testosterone have been noted to occur in men as they age. With regard to practice, the inverse relationship between protein and SHBG suggests that in elderly men a high protein diet could increase bioavailable testosterone and mitigate the effects of the age-related decrease in that hormone. Intervention studies will be necessary to verify this.

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