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Research Article

Frequency and Clinical Significance of Low or High Sex Hormone Binding Globulin Levels in Patients Suspected of Harboring Abnormal Testosterone Levels

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Abstract

Purpose: We aim to examine the frequency of low or high sex hormone binding globulin (SHBG) levels and to investigate whether they are associated with comorbidities and hormonal derangements in patients suspected of harboring abnormal testosterone levels.

Methods: This was a retrospective study of adult patients who underwent SHBG testing as part of a panel for testosterone at UCLA Health between May and July 2019.

Results: A total of 1102 male and 689 female patients underwent SHBG testing; the most common indications of the tests were suspected hypogonadism in male and hyperandrogenism in female patients. Eight male (0.7%, 9.4±1.0 nmol/L) and 66 female patients (9.6%, 21.7±5.2 nmol/L) exhibited low SHBG levels, and 113 male (10.3%, 106.6±29.6 nmol/L) and 118 female (17.1%, 187.1±59.6 nmol/L) patients exhibited high SHBG levels. Patients with low SHBG levels were younger, had higher body mass index, and less commonly receive sex hormone treatments than those with high SHBG levels but they were not different in other assessed clinical parameters. Bioavailable and free testosterone levels were not different in males with low or high SHBG levels but were significantly higher in females with low SHBG levels than in those with high SHBG levels.

Key words: sex hormone binding globulin; testosterone; sex hormones; comorbidities

Introduction

Sex hormone binding globulin (SHBG) is a transport protein that selectively binds with steroid hormones, especially androgens [1,2]. SHBG is made by the liver and released into the circulation. The only established clinical significance of SHBG is the regulation of bioavailable testosterone levels [3,4]. As SHBG binds with testosterone tightly, higher SHBG levels could reduce bioavailable testosterone levels while lower SHBG levels could raise bioavailable testosterone levels. Besides this function, SHBG may also play a role in the pathogenesis and pathophysiology of obesity, metabolic syndrome, polycystic ovary syndrome, osteoporosis, breast and prostate cancer, coronary artery disease, and aging [5-12]. SHBG levels are upregulated by estrogen, thyroid hormones, and antiepileptic drugs, in alcoholism, liver disease, HIV infection, and older age, and are downregulated by androgen, obesity, hyperinsulinemia, cortisol excess, progesterone use, growth hormone excess, nephrotic syndrome, and hypothyroidism [1-5,12-28]. It is not clear which of the known factors and what other potential factors are associated with low or high SHBG levels in routine clinical practice.

SHBG levels are commonly measured as a component of the testosterone panel which also includes total, bioavailable, and free testosterone. Thereby, low or high SHBG levels are found in some patients suspected of harboring abnormal testosterone levels, because SHBG results are reported with sex- and age-specific reference ranges. We are often asked by colleagues and patients about the clinical significance of low or high SHBG levels. The frequency and clinical significance of low or high

SHBG levels, however, are not known so far. In this study, we aim to examine the frequency of low or high SHBG levels and to investigate whether low or high SHBG levels are associated with comorbidities and hormonal derangements in patients suspected of harboring abnormal testosterone levels.

Methods

Patient Eligibility. All patients older than 18 years who were tested for SHBG at UCLA Health laboratory between May and July 2019 were eligible. There are no exclusion criteria. In all patients, SHBG levels were measured as a component of the testosterone panel which also included total, bioavailable, and free testosterone.

Data extraction. The list of patients was obtained from Department of Pathology and Laboratory Medicine, UCLA Health. The patients' electronic charts were accessed to gather information including demographics, clinical history, laboratory tests, imaging studies, surgical notes, and pathological reports. The patients' demographics, weight, height, body mass index, clinical presentation, bone density, alcohol drinking history, comorbidities, and laboratory test results were extracted. SHBG was measured by electrochemiluminescence immunoassay on the Roche Cobas e 602 platform. The SHBG reference ranges were 11-80 nmol/L for male and 30-135 nmol/L for female adult patients. Low SHBG levels were defined as values lower than the lower limits of normal reference ranges and high SHBG levels were defined as values higher than the upper limits of reference ranges.

Statistics. Continuous data were expressed as mean±SD in text or mean (range) in tables to provide more details. Student t test was used to determine the significance of the difference between the means of continuous values of two populations. Fisher's exact test was used to determine the significance of the difference between the rates of two populations.

Results

Frequency of low or high SHBG levels. Between May and July 2019, 1102 male and 689 female adult patients underwent SHBG testing as part of testosterone testing panel. Eight male (0.7%) and 66 female patients (9.6%) exhibited low SHBG levels, and 113 male (10.3%) and 118 (17.1%) female patients exhibited high SHBG levels (Table 1 and Table 2).

	Low SHBG	High SHBG	*p*
n	8	113	NA
Age (range), yr	46.0 (28-62)	63.3 (25-87)	<0.001
BMI (range), kg/m^2	31.0 (25.2-37.6)	25.1 (14.7-41.1)	<0.001
Testosterone replacement, yes/no, n	4/4	20/87	0.0577
Finasteride, yes/no, n	1/7	4/109	NS
Anastrozole, yes/no, n	0/8	1/112	NS
Estradiol, yes/no, n	0/8	3/110	NS
Liver disease, yes/no, n	0/8	5/102	NS
Alcohol drinking, yes/no, n	3/5	37/53	NS
Coronary artery disease, yes/no, n	1/7	9/104	NS
Osteoporosis, yes/no, n	0/8	3/110	NS
TSH (range), μIU/mL	3.4 (1.4-8.0) (n=6)	2.4 (0.02-18.5) (n=88)	NS
Prostate cancer, yes/no, n	1/7	7/106	NS
SHBG (range), nmol/L	9.4 (7-10)	106.6 (81-260)	<0.001
Total testosterone (range), ng/dL	226.3 (91-529)	615.0 (3-1531)	<0.001
Bioavailable testosterone (range), ng/dL	208.0 (72-434) (n=6)	160.2 (1-321) (n=98)	NS
Free testosterone (range), pg/mL	64.8 (25.3-141)	54.9 (0.6-126.6) (n=110)	NS
E2 (range), pg/mL	25.5 (16-35) (n=2)	73.8 (12-550) (n=19)	NS
LH (range), mIU/mL	7.5 (2.8-12) (n=2)	13.6 (0.1-56.1) (n=27)	NS
FSH (range), mIU/mL	7.8 (1.3-16.4) (n=3)	12.4 (0.1-51.3) (n=22)	NS
Prolactin (range), ng/mL	8.3 (7.3-9.3) (n=2)	41.0 (5-593) (n=21)	NS
AST (range), U/L	21.4 (16-32) (n=7)	26.5 (10-174) (n=93)	NS
ALT (range), U/L	27.3 (18-50) (n=7)	23.6 (7-310) (n=94)	NS
AP (range), U/L	68.1 (2-169) (n=7)	68.1 (37-135) (n=92)	NS
Bilirubin (range), mg/dL	0.5 (0.3-1) (n=7)	0.6 (0.2-2.1) (n=92)	NS
Albumin (range), g/dL	4.7 (4.2-5.3) (n=7)	4.4 (3.4-5.6) (n=92)	NS
Globulin (range), g/dL	2.8 (2.3-3.4) (n=7)	2.7 (1.8-4.6) (n=91)	NS

Table 1: Comparison of clinical characteristics of male adult patients with low or high SHBG levels. When data are not available for all patients, the number of patients with available data is indicated. The SHBG reference ranges were 11-80 nmol/L for male adult patients. NA, not applicable; NS, not significant.

	Low SHBG	High SHBG	*p*
n	66	118	NA
Age (range), yr	34.5 (18-74)	41.8 (18-75)	<0.001
BMI (range), kg/m^2	35.1 (21.3-53.4)	24.4 (16.6-38.6)	<0.001
Hormone replacement therapy, yes/no, n	4/62	22/96	0.0258
Hormonal contraception, yes/no, n	2/64	31/87	<0.001
Liver disease, yes/no, n	4/62	8/110	NS

Alcohol drinking, yes/no, n	25/29	53/45	NS
Polycystic ovary syndrome, yes/no, n	18/48	16/102	0.029
Coronary artery disease, yes/no, n	1/65	0/118	NS
Osteoporosis, yes/no, n	0/68	5/113	NS
TSH (range), µIU/mL	2.1 (0.2-10.7) (n=59)	2.1 (0.04-12.3) (n=97)	NS
Breast cancer, yes/no, n	0/66	1/117	NS
SHBG (range), nmol/L	21.7 (9-29)	187.1 (136-458)	<0.001
Total testosterone (range), ng/dL	31.8 (7-362)	42.1 (2-639) (n=114)	NS
Bioavailable testosterone (range), ng/dL	25.4 (3.6-207) (n=27)	4.0 (0.1-13.5) (n=31)	0.004
Free testosterone (range), pg/mL	6.8 (1.2-71)	2.1 (0.1-23.6) (n=113)	<0.001
E2 (range), pg/mL	57.5 (0-319) (n=28)	94.3 (0-820) (n=76)	NS
LH (range), mIU/mL	14.8 (2.1-64.7) (n=33)	14.6 (0-80.5) (n=47)	NS
FSH (range), mIU/mL	10.1 (2.8-108) (n=36)	23.7 (0-127) (n=65)	0.028
Prolactin (range), ng/mL	18.3 (6.6-53.1) (n=30)	16.0 (0-54.0) (n=36)	NS
AST (range), U/L	23.7 (10-57) (n=46)	56.7 (10-2661) (n=79)	NS
ALT (range), U/L	30.4 (11-143) (n=46)	44.2 (8-1819) (n=80)	NS
AP (range), U/L	75.1 (49-160) (n=46)	64.7 (25-255) (n=78)	NS
Bilirubin (range), mg/dL	0.42 (0.2-1.1) (n=44)	0.45 (0.2-2) (n=77)	NS
Albumin (range), g/dL	4.6 (4-5.3) (n=46)	4.5 (3.2-5.3) (n=76)	NS
Globulin (range), g/dL	3.0 (1.7-4.0) (n=45)	2.7 (1.7-4.0) (n=78)	0.001

Table 2: Comparison of clinical characteristics of female adult patients with low or high SHBG levels. When data are not available for all patients, the number of patients with available data is indicated. The SHBG reference ranges were 30-135 nmol/L for female adult patients. NA, not applicable; NS, not significant.

Characteristics of patients with low or high SHBG levels. The mean SHBG level of male patients with low SHBG levels was 9.4±1.0 nmol/L and that with high SHBG levels was 106.6±29.6 nmol/L. The mean SHBG level of female patients with low SHBG levels was 21.7±5.2 nmol/L and that with high SHBG levels was 187.1±59.6 nmol/L (Table 1 and Table 2). In both male and female patients, those with low SHBG levels were younger (mean age 46.0 versus 63.3 in male patients, $p<0.001$; and 34.5 versus 41.8 in female patients, $p<0.001$) and had higher BMI (mean BMI 31.0 versus 25.1 in male patients, $p<0.001$; and 35.1 versus 24.4 in female patients, $p<0.001$). Male patients with high SHBG levels tend to be more frequently on testosterone replacement than those with low SHBG levels but the difference was not quite significant. Female patients with high SHBG levels, however, were clearly more frequently on hormone replacement or hormonal contraception than those with low SHBG levels. Use of finasteride, anastrozole, and estradiol was rare and not different in male patients with low or high SHBG levels. History of liver disease, alcohol drinking, coronary artery disease, and osteoporosis and TSH were not different in either male or female patients with low or high SHBG levels. History of prostate cancer was not different in male patients with low or high SHBG levels, neither was history of breast cancer in female patients. Eighteen of the 66 female patients (27.3%) with low SHBG levels had polycystic ovary syndrome, significantly more often than those in the high SHBG group (16 of 118 patients, 13.6%). As expected, total testosterone levels were significantly lower in male patients with low SHBG levels than in those with high SHBG levels (226.3 versus 615.0 ng/dL, $p<0.001$) but bioavailable and free testosterone levels were not significantly different. Total testosterone levels were approximately similar in female patients with low or high SHBG levels (31.6 versus 42.1 ng/dL) but bioavailable and free testosterone levels were significantly higher in those with low SHBG (25.4 versus 4.0 ng/dL, $p=0.004$ and 6.8 versus 2.1 pg/mL, $p<0.001$, respectively). Estradiol, LH, FSH, and prolactin levels were not significantly different in male patients with low or high SHBG levels. Estradiol, LH, and prolactin levels were not significantly different in female patients with low or high SHBG levels but FSH levels were significantly higher in female patients with high SHBG levels (who were also 7 years older). Liver function tests results were largely similar between both male and female patients with low or high SHBG levels. We did not have systemic data on seizure, antiepileptic medications, corticosteroid use, HIV infection, nephrotic syndrome, insulin levels, or growth hormone status in these patient groups.

Hypogonadism and erectile dysfunction were the most common conditions in male patients with SHBG tests (Table 3 and Table 4). Because only 8 males had low SHBG levels, it was impossible to derive medical factors within this group that are associated with low SHBG levels. In male patients with high SHBG levels, 3 treated with estrogen for transgender purposes had the highest SHBG as a group (Table 4). Male patients with prostate cancer who were undergoing androgen ablation therapy had higher SHBG levels than those who were not but the difference was not significant, likely due to small sample size (Table 4).

Indication	n (%)	Age, mean (range), yr*	SHBG, mean (range), nmol/L*
Hypogonadism	7 (87.5)	46.9 (28-62)	9.3 (7-10)
Erectile dysfunction	1 (12.5)	40	10

Table 3: Clinical characteristics of male patients with low SHBG levels. *When an indication only applies to 1 patient, the individual values are listed.

Indication	n (%)	Age, mean (range), yr*	SHBG, mean (range), nmol/L*
Hypogonadism	33 (29.2)	64.3 (29-87)	102.6 (82-175)
Erectile dysfunction	15 (13.2)	61.8 (35-84)	109.3 (85-260)
Health maintenance	13 (11.5)	57.8 (30-78)	118.4 (82-186)
Prostate cancer	9 (8.0)	74.6 (54-84)	98.0 (81-140)

Prostate cancer without androgen ablation	5 (4.4)	70.6 (54-80)	93.2 (81-105)
Prostate cancer with androgen ablation	4 (3.5)	79.5 (73-84)	104.0 (81-140)
Fatigue	8 (7.1)	49.9 (38-76)	100.4 (82-122)
Osteoporosis	7 (6.0)	68.7 (55-78)	114.1 (86-144)
Benign prostate hypertrophy	6 (6.2)	72.2 (62-80)	92.3 (86-106)
Low libido	4 (3.5)	64.5 (59-67)	95.3 (84-113)
Gynecomastia	3 (2.7)	58.3 (25-80)	96.7 (84-106)
Male-to-female transgender	3 (2.7)	56.0 (47-65)	182.3 (166-191)
Pituitary tumor	3 (2.7)	60.3 (44-74)	106.0 (86-131)
Anemia	2 (1.8)	66, 69	83, 103
Family history of high testosterone	1 (0.9)	82	83
Alopecia	1 (0.9)	56	87
Adrenal cortical carcinoma	1 (0.9)	53	89
Not described	4 (3.5)	63 (57-69)	111.8 (88-156)

Table 4: Clinical characteristics of male patients with high SHBG levels. *When an indication only applies to 1 or 2 patients, the individual values are listed.

Polycystic ovary syndrome, irregular menses, and hirsutism were the most common conditions in female patients with low SHBG levels (Table 5). The SHBG levels were remarkably similar regardless of the clinical conditions in female patients with low SHBG levels. Menopause, irregular menses, and polycystic ovary syndrome were the most common conditions in female patients with high SHBG levels (Table 6). The 17 patients with polycystic ovary syndrome had the highest SHBG levels as a group but the difference between the SHBG levels in female patients with polycystic ovary syndrome and those in other groups was small.

Indication	N (%)	Age, mean (range), yr*	SHBG, mean (range), nmol/L*
Polycystic ovary syndrome	29 (43.9)	28.5 (18-54)	20.7 (9-29)
Irregular menses	8 (12.1)	33.3 (22-39)	21.4 (16-25)
Hirsutism	6 (9.1)	35.7 (19-58)	23.0 (16-29)
Amenorrhea	5 (7.6)	27.0 (20-44)	20.4 (14-29)
Menopause	5 (7.6)	49.8 (41-47)	24.2 (21-29)
Hyperandrogenism	4 (6.1)	63.5 (54-74)	22.3 (14-28)
Alopecia	3 (4.5)	30.3 (19-41)	22.7 (19-25)
Female-to-male transgender	1 (1.5)	47	27
Infertility	1 (1.5)	39	24
Not described	4 (6.1)	38.5 (20-63)	22.3 (9-29)

Table 5: Clinical characteristics of female patients with low SHBG levels. *When an indication only applies to 1 or 2 patients, the individual values are listed.

Indication	n (%)	Age, mean (range), yr*	SHBG, mean (range), nmol/L*
Menopause	34 (28.8)	52.4 (40-75)	175.6 (136-312)
Irregular menses	17 (14.4)	33.3 (18-63)	171.8 (137-251)
Polycystic ovary syndrome	17 (14.4)	28.4 (19-39)	214.8 (138-358)
Alopecia	7 (5.9)	46.4 (27-67)	194.1 (141-385)
Low libido	5 (4.2)	47.2 (36-57)	191.2 (142-292)
Amenorrhea	4 (3.4)	35.0 (28-39)	170.5 (160-178)
Hirsutism	3 (2.5)	34.3 (25-44)	159.3 (143-170)
Acne	3 (2.5)	42.7 (25-61)	151.0 (142-168)
Hormone imbalance	3 (2.5)	39.0 (31-47)	198.7 (143-281)
Healthcare maintenance	2 (1.7)	27, 31	161, 236
Hyperandrogenism	2 (1.7)	29, 43	168, 173
Fatigue	2 (1.7)	39, 56	164, 456
Pelvic pain	1 (0.8)	50	139
Pregnancy	1 (0.8)	36	380
Premenstrual syndrome	1 (0.8)	42	151
Female-to-male transgender	1 (0.8)	25	140
Low testosterone	1 (0.8)	39	169
Ovarian cyst	1 (0.8)	51	178
Dyspareunia	1 (0.8)	31	197
Endometriosis	1 (0.8)	34	186
Cushing disease	1 (0.8)	23	331

Anovulation	1 (0.8)	34	145
Adrenal mass	1 (0.8)	71	214
Chest pain	1 (0.8)	56	259
Headache	1 (0.8)	38	165
Not described	6 (5.1)	50.3 (25-63)	166.7 (148-183)

Table 6: Clinical characteristics of female patients with high SHBG levels. *When an indication only applies to 1 or 2 patients, the individual values are listed.

Discussion

Whenever an abnormal test result is reported, its clinical significance becomes the key issue. After sex hormone binding globulin (SHBG) was routinely reported as part of a testosterone panel in our institution, we began to encounter low or high SHBG levels defined by the clinical laboratory. We were also asked by patients on why their SHBG levels were low or high and how to make the SHBG levels normal. Our current study gives us useful information on the clinical significance of low or high SHBG levels in patients suspected of harboring abnormal testosterone levels.

Most studies classify SHBG levels into tertiles or quartiles, implying that no abnormal SHBG levels are defined [18,27,28]. In a clinical setting, all laboratory tests, including SHBG, must have a reference range. To our knowledge, the frequency of low or high SHBG levels in a clinical setting has not been reported before. We first show that in patients with suspected testosterone abnormalities, mostly hypogonadism in males and hyperandrogenism in females, low SHBG levels are rare in males but quite common in females (about 10%) and high SHBG levels are quite common in both males (about 10%) and females (about 17%). Thus overall, over 10% of males with suspected hypogonadism and over 25% of females with suspected hyperandrogenism have "abnormal" SHBG levels, making SHBG result interpretation a significant issue for those patients in clinical practice. It is worthwhile to point out that our results on frequency of low or high SHBG levels in our study subjects were limited to patients suspected of harboring abnormal testosterone levels and should not be extrapolated to other population without further studies.

The biological functions of SHBG are complex and appear to be involved in many metabolic processes such as sex hormone function, obesity, metabolic syndrome, polycystic ovary syndrome, osteoporosis, breast and prostate cancer, coronary artery disease, and aging [1-12]. The diverse functions of SHBG are either mediated through modulation of sex hormone function or through direct SHBG interaction with its target cells [1-4,29]. Having "abnormal" SHBG levels is therefore a potentially large health hazard. Our data, however, show that "abnormal" SHBG levels have limited health effects. Male and female patients appear to have a somewhat different response to low or high SHBG levels. In male patients, even though total testosterone levels are higher in those with high SHBG levels, bioavailable and free testosterone levels are not different between those with low or high SHBG levels. Our data suggest that male patients with high SHBG levels may be more likely to received testosterone treatment, which increase the bioavailable and free testosterone levels in those patients as a group. In female patients, however, bioavailable and free testosterone levels are higher in those with low SHBG levels. Although we don't have clear evidence indicating a specific mechanism for the difference in androgen response to SHBG levels in male and female patients, the higher gonadotropin levels in male patients with high SHBG levels suggests that male patients could compensate for the high SHBG levels by raising gonadotropin levels to stimulate testosterone production. This hypothesis needs to be tested in future studies. The very similar LH levels in female patients with low or high SHBG levels suggests that the higher FSH levels in female patients with high SHBG levels are probably due to the older age. Apart from testosterone levels, we did not find any difference in the association of low or high SHBG levels with polycystic ovary syndrome, osteoporosis, breast and prostate cancer, or coronary artery disease.

The regulation of SHBG levels is not very well understood [1-4,30,31]. Our study confirms that high SHBG levels are associated with older age and low SHBG levels with obesity in both male and female patients [5-12]. Our results are also generally consistent with the well-established observations that estrogen raises, and androgen suppresses, SHBG levels. Our data clearly showed that female patients with high SHBG levels more frequently were on hormone replacement therapy or hormonal contraception than those with low SHBG levels. The statistical trend of more frequent testosterone replacement in male patients with high SHBG than those with low SHBG levels is more plausibly explained by that the male patients with high SHBG levels tend to harbor lower bioavailable and free testosterone levels thus were more likely to require testosterone replacement. Alcohol drinking and withdrawal are associated with high SHBG levels [15, 16]. In our patient population, however, the percentage of patients with alcohol drinking history is not different between male and female patients with low or high SHBG levels, implying that alcohol drinking is not a major factor influencing SHBG levels in clinical practice. High SHBG levels are also associated with liver diseases such as iron overload and nonalcoholic fatty liver disease [17,18]. Liver functions and established liver diseases were remarkably similar in both male and female patients with low or high SHBG levels in our study, arguing against that liver disease is a major factor influencing SHBG levels in clinical practice. Although thyroid hormones regulate SHBG levels [13-26], the differences in SHBG levels in our patients were not explained by differences in the thyroid status as TSH levels were similar in both male and female patients with low or high SHBG levels. We did not have systemic data on seizure, antiepileptic medications, corticosteroid use, HIV infection, nephrotic syndrome, insulin levels, or growth hormone status which regulate SHBG levels [14,19-25]; case studies, however, did not find any of the factors we did not systemically study were present in those patients with the lowest or highest SHBG levels (data not shown). The major factors determining SHBG levels may be heterogeneous and remain unclear.

Our study had several limits. It was descriptive and correlative based on available clinical, laboratory, and imaging data. We could not derive convincing causal-effective relationship between the studied parameters and SHBG levels. Missing data prevented us from doing multivariate analysis of the numerous factors potentially correlated with SHBG levels. Our study did not collect data on patients with normal SHBG levels because we reasoned that if SHBG levels are associated with a particular disease, it is mostly likely to be differentially present in patients with low or high SHBG levels. Nonetheless, lack of data of patients with normal SHBG levels was still a limit of our study. Lastly, we could only study factors that we suspect may be correlated with SHBG levels or that we had data on so that we could miss factors that are significantly correlated with SHBG levels.

In summary, our study shows that low or high SHBG levels are common in patients suspected of harboring abnormal testosterone levels, especially in female patients. Besides age, body mass index, and sex hormone treatment, no other clinical characteristics are found to be correlated with SHBG levels in patients suspected of harboring abnormal testosterone levels. SHBG levels are not significantly associated with bioavailable and

free testosterone levels in males but are inversely associated with bioavailable and free testosterone levels in females. Regardless of the causes, low or high SHBG levels per se do not appear to be a health hazard.

Compliance with Ethical Standards

Conflicts of interests:

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval:

The study has been approved by the UCLA Institution Review Board (#20-000631).

Informed Consent:

Informed Consent was waived by the UCLA Institution Review Board.

Conclusions: Low or high SHBG levels are common in patients suspected of harboring abnormal testosterone levels. Besides age, body mass index, and sex hormone treatments, no other clinical characteristics are found to be correlated with SHBG levels in this patient population.

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