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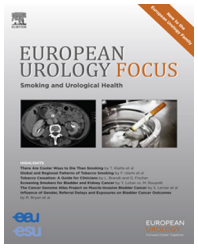

Andrology

Serum Concentrations of Sex Hormone–binding Globulin Vary Widely in Younger and Older Men: Clinical Data from a Men's Health Practice

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Abstract

Background: The testosterone (T) status of a man is influenced by serum concentrations of sex hormone–binding globulin (SHBG). Specifically, tight binding of T to SHBG is believed to render the SHBG-bound T fraction biologically unavailable, meaning that interpretation of T levels in the clinical setting depends in part on knowledge of SHBG concentrations. Although SHBG levels have been reported in population studies, there is scant information for men presenting with clinical symptoms.
Objective: To report SHBG values for a large cohort of men presenting to a men's health center.
Design, setting, and participants: Medical records were reviewed for 1000 consecutive patients seen at our center with a reported SHBG value. SHBG concentrations were measured by a national clinical laboratory using an immunoassay run on a Beckman Coulter DXi system.
Outcome measurements and statistical analysis: Patients were age-stratified and data were plotted in the form of comparative histograms.
Results and limitations: The mean age (± standard deviation) of the total cohort was 53.5 ± 13.5 yr (range 17–91). The mean SHBG was 31.8 ± 15.2 nmol/l (range 6-109), with a nearly 20-fold difference from the lowest to the highest values. SHBG was >60 nmol/l in 5.6% of the men. Patients were stratified according to age. A total of 535 patients were ≤54 yr old. In this younger cohort, the mean age was 40.52 ± 7.9 yr (range 17–54) and mean SHBG was 27.7 ± 13.3 nmol/l (range 6–88), and 2.2% of patients had SHBG >60 nmol/l. A total of 465 patients were ≥55 yr old. In this older cohort, the mean age was 64.8 ± 7.23 yr (range 55–91) and mean SHBG was 36.6 ± 15.8 nmol/l (range 11–109), and 9% of patients had SHBG >60 nmol/l. Mean SHBG was significantly higher in the older group ($p < 0.001$).
Conclusions: A remarkably wide distribution of SHBG concentrations was observed in a clinical population of men presenting to a men's health center, among both younger and older men. Since SHBG concentrations greatly influence test results for hormones that bind to SHBG, recognition of this large interindividual variability should be considered in the clinical interpretation of these hormone results, particularly for T. Routine SHBG testing should be considered for men suspected of T deficiency.
Patient summary: Sex hormone–binding globulin (SHBG) levels vary widely among both older and younger men. This may impact the interpretation of test results for hormones that bind to SHBG, such as testosterone, since the portion that binds to SHBG is believed to not be biologically available.

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1. Introduction

Sex hormone–binding globulin (SHBG) is a glycoprotein synthesized in the liver that demonstrates high-affinity binding to testosterone (T), dihydrotestosterone, and estradiol [1]. As a sex steroid carrier molecule, SHBG plays a critical role in T physiology. Some 60% of circulating T is tightly bound to SHBG, with the rest either loosely bound to albumin or circulating as free T (FT). High-affinity binding of T to SHBG renders this fraction biologically inactive, as the normally lipophilic T is unable to diffuse through cell membranes when bound to SHBG. This relationship of T to SHBG is of considerable importance in clinical practice, since SHBG-bound T represents a major proportion of total T (TT) measured, considered the standard test to identify men with T deficiency (also called hypogonadism). Variations in SHBG will therefore greatly impact the diagnosis of T deficiency.

Studies have demonstrated that obesity, aging, acromegaly, human immunodeficiency virus, thyroid disease, and certain medications alter serum SHBG concentrations [2]. Conditions associated with increased or decreased SHBG concentrations are presented in Table 1. A variety of studies have explored SHBG concentrations as predictors of subsequent development of metabolic conditions and cardiovascular disease, with SHBG emerging as a metabolic parameter of increasing interest. Most studies have concluded that patients with lower SHBG levels are at higher risk of subsequent metabolic syndrome and type 2 diabetes (T2DM) [3]. It has been demonstrated that low SHBG levels are a risk factor for T2DM development among school-aged girls over the course of 10 yr [4]. Three large meta-analyses all demonstrated that lower SHBG levels are independent risk factors for subsequent development of T2DM [5–7].

While the bulk of the research has explored SHBG as a predictor of metabolic disease, studies have also demonstrated other physiologic processes related to altered SHBG concentrations. Thyroid hormones directly stimulate SHBG synthesis in the liver, and patients with hyperthyroidism often have elevated serum SHBG [8]. Conversely, prolactin has an inhibitory effect on SHBG synthesis, leading to lower serum concentrations [9]. Hyperinsulinemia, seen both in acromegaly and in iatrogenic settings, decreases serum SHBG. Cirrhosis is associated with higher SHBG levels [10], but liver transplantation decreases levels to within normal limits [11]. There is solid evidence from multiple studies that SHBG concentrations increase with age. The European Male Aging Study demonstrated that mean SHBG increases by approximately 50% from 40 yr to 75 yr [12]. For any given TT concentration, higher SHBG levels means that there are lower concentrations of albumin-bound and FT, which together represent the bioavailable T fraction. There is limited information regarding the variability of serum SHBG distributions in clinical populations of men in whom SHBG concentrations may impact medical decision-making, namely in men who may have T deficiency.

The aim of this study was to investigate the distribution of serum SHBG across a large cohort of men presenting to a men's health practice with sexual concerns.

Table 1 – Conditions that impact sex hormone–binding globulin (SHBG) values.

Conditions that decrease SHBG	Conditions that increase SHBG
Obesity	Aging
Hypothyroidism	Cirrhosis
Steroid use	Estrogen use
Nephrotic syndrome	Human immunodeficiency virus
Acromegaly	Anticonvulsant use
Progesterone use	Hyperthyroidism
Insulin use	Androgen use

2. Patients and methods

Electronic medical records were reviewed using eClinical Works for the last 1000 men with a reported SHBG seen at our center. Testing for SHBG is routinely performed at our center for men with sexual complaints, including erectile dysfunction, low libido, T deficiency, Peyronie's disease, and ejaculatory disorders. When multiple SHBG values were available, only the first SHBG was used in our analysis. All SHBG measurements were performed by a national laboratory (Quest Diagnostics Laboratory) using an immunoassay (chemiluminescent substrate Lumi-Phos 530) run on a Beckman Coulter DXi system. The assay is validated internally and at SJC California.

Patients were age-stratified and data were plotted in the form of comparative histograms. Student's *t* test was used to test for significance between means. The Kolmogorov-Smirnov test was used to test for normal distribution. We used 60 nmol/l as the upper limit of normal, corresponding to the laboratory's upper reference value for younger men (range 20–60 nmol/l). A normal distribution without significant skewness was noted for all SHBG assessments.

3. Results

Table 2 presents information on our study population. The overall cohort of 1000 patients was divided into younger and older groups, using 55 yr as a convenient value that provided approximately equal numbers for each group. There were 535 men aged $\leq$55 yr and 465 men aged $\geq$55 yr. A recent internal census has revealed that our clinical population has a mean body mass index of 28.9 kg/m^2, with hypertension and diabetes rates of 34% and 13%, respectively. Demographically, our clinical population is 70% Caucasian, 14% Black, 10% Asian, and 6% American Indian.

The mean age ($\pm$ standard deviation) of the total cohort was 53.5 y $\pm$ 13.5 yr (range 17–91). Mean SHBG for the total cohort was 31.8 $\pm$ 15.2 nmol/l (6–109). SHBG levels above the upper reference value of 60 nmol/l were noted in 5.6% of the total cohort (Fig. 1). The range of values within one standard deviation of the mean varied nearly threefold, from approximately 16 to 46 nmol/l.

The mean age in the younger cohort was 40.5 $\pm$ 7.9 yr (range 17–54) and mean SHBG was 27.7 $\pm$ 13.3 nmol/l (range 6–88). A histogram of the SHBG distribution in this population is shown in Fig. 2. Elevated SHBG levels were noted in 2.2% of this cohort. The median value was 25 nmol/l, and the mode was 20 nmol/l.

The mean age in the older cohort was 64.8 $\pm$ 7.23 yr (range 55–91) and mean SHBG was 36.6 $\pm$ 15.8 nmol/l

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Table 2 – Serum sex hormone–binding globulin (SHBG) by age.

Cohort	Men	Age (yr)		SHBG (nmol/l)		*p* value
	(*n*)	Mean (SD)	Range	Mean (SD)	Range	
All ages	1000	53.5 (13.5)	17–91	31.8 (15.2)	6–109	
Men aged ≤54 yr	535	40.5 (7.9)	17–64	27.7 (13.3)	6–88	
Men aged ≥55 yr	465	64.8 (7.23)	55–91	36.6 (15.8)	11–109	<0.001

SD = standard deviation.

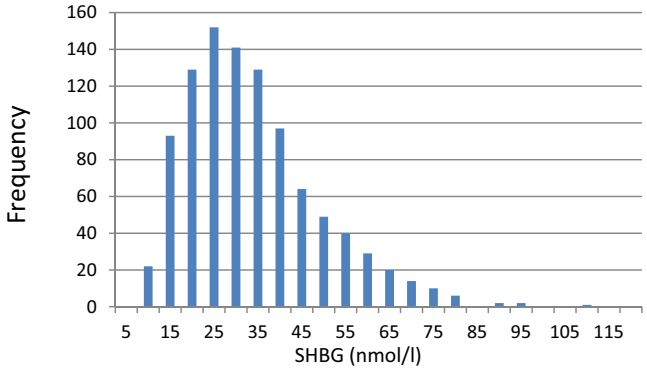

Fig. 1 – Histogram of sex hormone–binding globulin (SHBG) values among men of all ages (*n* = 1000).

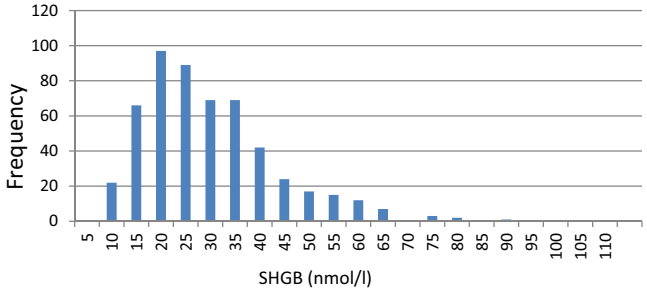

Fig. 2 – Histogram of sex hormone–binding globulin (SHBG) values among men aged ≤54 yr (*n* = 535).

(range 11–109). A histogram of the SHBG distribution in this population is shown in Fig. 3. Elevated SHBG levels were noted in 9.0% of men in the older cohort. The median value was 33 nmol/l, and the mode was 29 nmol/l.

The distribution of mean SHBG values by decade is presented in Fig. 4. Comparison of younger and older

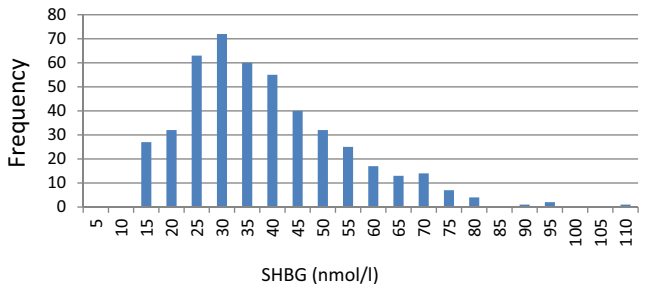

Fig. 3 – Histogram of sex hormone–binding globulin (SHBG) values among men aged ≥55 yr (*n* = 465).

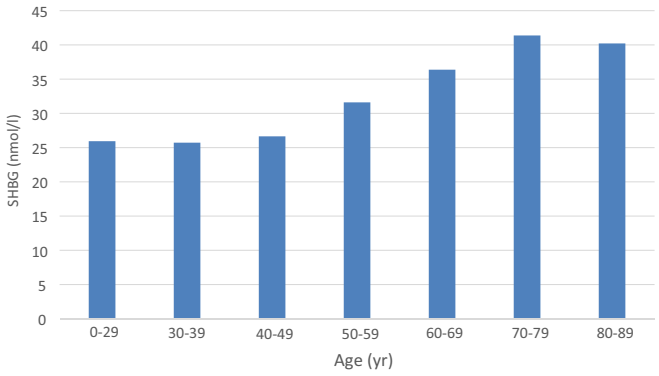

Fig. 4 – Mean sex hormone–binding globulin (SHBG) values by decade.

cohorts revealed that mean SHBG was significantly higher in the older group ($p < 0.001$). In addition, the percentage of men with elevated SHBG was also significantly greater among older men ($p < 0.001$).

4. Discussion

Numerous studies have investigated the association between serum SHBG and various conditions, including metabolic syndrome, cardiovascular disease, and bone disease. However, there is scant information regarding the distribution of SHBG concentrations in clinical practice, particularly among men with sexual symptoms who may have T deficiency. In these men, low or elevated SHBG concentrations may influence interpretation of TT concentrations. To the best of our knowledge, this is the first study to provide detailed SHBG values for a large clinical population of men presenting specifically with sexual symptoms.

In this study we found wide interindividual variability in SHBG concentrations. There was a nearly 20-fold difference in values over the range of SHBG results, and an approximately threefold difference merely within one standard deviation from the mean. Consistent with previous studies, younger men had lower mean SHBG concentrations than older men, yet wide variability in results were seen for both younger and older men. Values above the upper reference value were noted in 2.2% of men aged ≤54 yr, and in 9% of men aged ≥55 yr.

Our results for SHBG concentrations are relatively consistent with the literature (Table 3). Chubb et al [13] found that the average SHBG in a population of 2490 healthy, nondiabetic men (mean age 76 yr) was 43.0 ± 15.6 nmol/l.

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Table 3 – Percentage of patients with sex hormone–binding globulin (SHBG) >60 nmol/l.

Cohort	Men (*n*)	Men with SHBG >60 nmol/l (%)
All ages	1000	5.6
Men aged ≤54 yr	535	2.2
Men aged ≥55 yr	465	9.0

Ukkola et al [14] analyzed the HERITAGE family study database, largely consisting of younger men, and reported average SHBG of 38.4 ± 16.5 nmol/l. Similar results were published for a Finnish population cohort, with mean SHBG of 38.1 ± 16.0 nmol/l. Table 4 summarizes the literature reporting mean SHBG values in large studies. The variability in mean SHBG across studies can be attributed to differences in mean age (Fig. 5) and the type of cohort being evaluated. For example, using the Massachusetts Male Ageing Study (*n* = 1096, mean age 53 yr) to explore the relationship between SHBG and metabolic syndrome, Kupelian et al [15] reported average SHBG of 26.1 ± 11.8 nmol/l among men with metabolic syndrome and 33.6 ± 16.1 nmol/l among men without metabolic syndrome. The

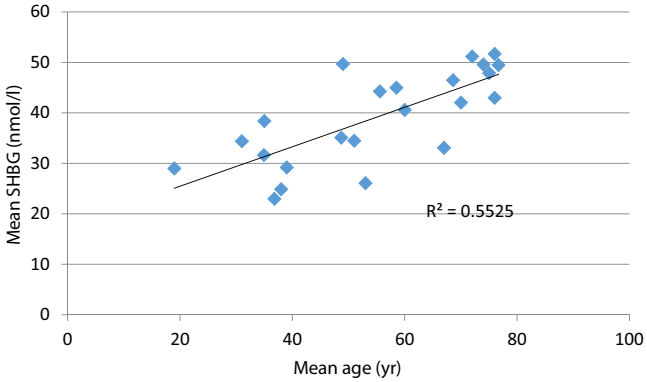

Fig. 5 – Mean sex hormone–binding globulin (SHBG) versus mean age in population-based studies (each data point represents a different study).

literature to date has demonstrated the variability of serum SHBG values but has not specifically reported detailed SHBG distributions among men with sexual symptoms.

The influence of SHBG on T measurement and physiology was recently explored in a set of elegant experiments using a mouse model [16]. Mice and rats do not normally express SHBG, and circulating serum T concentrations are a fraction

Table 4 – Studies reporting average SHBG values.

Study	Year	Men (*n*)	Mean age (yr)	Population	SHBG, nmol/l (SD)
Jaspers [19]	2016	1647	68.6	Rotterdam Study, PS	46.5
Li [20]	2016	969	40–80	Chinese men, PS	43.3
Travison [21]	2016		50 (±10)	Framingham, PS	55 (27)
Kische [22]	2016	204	48.7	Sleep study	35.1
Jensen [23]	2016	652	19.0	Danish, healthy men	29
Woods [24]	2016	1500	65+	PS	49.1 (19.7)
Shen [25]	2016	227 (young men) 939 (older men)	34.9 (young men) 44.67 (older men)	Chinese PS	31.7 (14.6) young 44.27 (20.6) older
Orwoll [26]	2016	1476	72	Hong Kong population	51.2 (20.4)
			74	US population	49.6 (20)
			75	Swedish population	47.9 (22.1)
Atonio [27]	2015	1651	58.5	EMAS	45
Hsu [28]	2014	1299	76.7	Population based	49.5 (21)
Macdonald [29]	2013	511	36.8	Men at a fertility clinic	23.0 (12)
Haring [30]	2013	1906	20–79	PS	49.8
Milewicz [31]	2013	4352	76	Polish men, PS	51.7
Maggio [32]	2013	430	70	Prospective Study of the Vasculature in Uppsala Seniors	42.1
Chen [33]	2010	206			37.0 (15.3)
Stefan [34]	2009	1004	49	PS	49.7 (20.6)
Chubb [13]	2008	2490	76	Non-diabetic men, Health in Men Study	43.0 (15.6)
Corona [35]	2008	558	NR		35.7 (16.6)
Emmelot-Vonk [36]	2008	200	67	Men with low normal testosterone	33.1 (10.3)
Goncharov [37]	2008	60	31	Obese men	34.4 (22.8)
Onat [47]	2007	536	NR	NR	44.6 (20.4)
Kupelian [15]	2006	1096	53	Massachusetts Male Ageing Study	26.1 (11.8)
Mohr [38]	2006	1709	40–70	PS	35.2 (16.7)
Gannage-Yared [39]	2006	152	NR	PS	36.7 (14.8)
Muller [40]	2005	374	60	PS	40.6 (14.4)
Nuver [41]	2005	161	38	Postchemotherapy patients	24.9 (10.1)
Unden [42]	2005	137	NR	PS	44.5 (21.9)
Tong [43]	2005	295	39	Hong Kong Family diabetes study	29.2 (13.2)
Laukkanen [44]	2004	702	51	Kuopio Ischaemic Heart Disease Risk Factor Study	34.5 (16.6)
Hautanen [45]	2000	96	NR	Finnish PS	38.1 (16.0)
Ukkola [14]	2001	855	35	HERITAGE study	38.4 (16.5)
Phillips [46]	1993	55	21–70	Obese men	19.3 (8.2)

SHBG = sex hormone–binding globulin; SD = standard deviation; PS = population study; NR = not reported.

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of human concentrations. On experimental introduction of a transgenic SHBG protein, serum T concentrations substantially increased, yet FT concentrations decreased. Seminal vesicle size was reduced compared to wild-type mice, indicating a hypogonadal state. The authors concluded that these experiments provide strong evidence that higher SHBG raises serum T, and that androgen action depends primarily on FT concentrations as the bioactive fraction.

In 2014, Vos et al [17] reported on a family with a missense mutation in the *SHBG* gene, resulting in two individuals—one male and one female—with complete SHBG deficiency. The male presented at 27 yr with a nonspecific history of fatigue and weakness. His SHBG concentration was undetectable, TT was low, and FT levels were within the normal range. Sexual development and spermatogenesis were normal. The authors concluded that the man's normal sexual development must have occurred as a result of his normal FT concentration. The discrepancy between the patient's low TT and normal FT can be explained by the complete absence of SHBG to bind T and render it inactive. This case demonstrates that low SHBG may result in apparent low TT in individuals with normal androgen status. Reliance on TT without consideration of SHBG concentrations may lead clinicians to categorize individuals as T-deficient when they are in fact eugonadal.

Variation in SHBG concentrations may have an important impact on the interpretation of blood test results in clinical medicine, particularly for T. In a recent study of 3334 men aged 40–79 yr, low calculated FT correlated more strongly than TT with regard to symptoms of androgen deficiency [12]. In this study, men with normal TT together with low FT had higher SHBG concentrations. Interestingly, men with low TT but normal FT were unlikely to have symptoms. This underscores the importance of FT concentrations in evaluating the androgen status of a patient, which in turn is dependent on knowing the SHBG concentration. Men with normal TT and low FT were significantly older (68.4 vs 58.9 yr) than men with normal TT and normal FT and had significantly higher serum SHBG (58.1 vs 43.2 nmol/l).

One of the known causes of increased SHBG is aging. In the current study, mean SHBG was 36.6 nmol/l among men aged $\geq$55 yr (mean age 64.8) compared to 27.7 nmol/l for men aged $\leq$54 yr (mean age 40.5). In addition, the percentage of men with SHBG above the upper reference value was greater in the older (9.0%) than in the younger group (2.2%). Data from the European Male Aging Study demonstrate a steady rise in SHBG with increasing age among men aged from 40 yr to >70 yr [18]. Fig. 4 demonstrates the correlation between increasing age and SHBG on the basis of 24 large-scale studies. The clinical relevance of elevated SHBG is that TT concentrations may appear normal in T-deficient men whose symptoms result from low FT values. We note that comorbidities may influence SHBG concentrations, in addition to age (Table 1).

These results support recommendations by a number of professional societies to test for SHBG concentrations to calculate FT concentrations for men whose clinical presentation is at odds with their TT concentrations. An online FT calculator has been provided by the International Society for the Study of the Aging Male at www.issam.ch/freetesto.htm. Results are obtained by inputting TT and SHBG concentrations. Albumin is usually assumed to be 4.3 g/dl. The impact of SHBG variability on FT concentrations can be demonstrated using this calculator. For example, for TT of 350 ng/dl, changing the SHBG concentration from 20 to 60 nmol/l reduces the FT concentration by nearly half, from 9.08 ng/dl (91 pg/ml) to 4.68 ng/dl (47 pg/ml). Even though these SHBG values are both within the normal range, the impact of this variability on FT concentrations is substantial. The first FT value would be considered well within the normal range by most authorities, whereas the second is unequivocally low.

The strengths of this study include its large size, SHBG measurement by a single, national laboratory, and measurement in an appropriate clinical population, namely, men presenting with sexual complaints. The limitations of the study include the fact that this population of men sought consultation largely for sexual symptoms. These results may not be generalizable to other populations. In addition, the results were obtained from a laboratory database without clinical correlation, such as the presence of comorbidities beyond diabetes and hypertension, symptoms of T deficiency, or other items of clinical interest that may influence SHBG concentrations.

5. Conclusions

In a large population of men presenting to a men's health clinic with sexual concerns, we found a wide distribution of SHBG among both younger and older men. This wide variability in SHBG concentrations should be considered in the clinical interpretation of test results for hormones that bind to SHBG, in particular testosterone.

Author contributions: Abraham Morgentaler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Morgentaler, Krakowsky, Conners.
Acquisition of data: Krakowsky.
Analysis and interpretation of data: Morgentaler, Krakowsky, Conners.
Drafting of the manuscript: Morgentaler, Krakowsky, Conners.
Critical revision of the manuscript for important intellectual content: Morgentaler, Krakowsky, Conners.
Statistical analysis: Morgentaler, Krakowsky.
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Supervision: None.
Other: None.

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Medical Systems. William Conners has received consultancy/advisory fees from Eli Lilly. Yonah Krakowsky has nothing to disclose.

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References

[1] Coviello AD, Haring R, Wellons M, et al. A genome-wide association meta-analysis of circulating sex hormone-binding globulin reveals multiple loci implicated in sex steroid hormone regulation. PLoS Genet 2012;8:e1002805. http://dx.doi.org/10.1371/journal.pgen.1002805.

[2] Hammond GL. Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. J Endocrinol 2016;230:R13–25. http://dx.doi.org/10.1530/JOE-16-0070.

[3] Le TN, Nestler JE, Strauss JF, Wickham EP. Sex hormone-binding globulin and type 2 diabetes mellitus. Trends Endocrinol Metab 2012;23:32–40. http://dx.doi.org/10.1016/j.tem.2011.09.005.

[4] Glueck CJ, Morrison JA, Daniels S, Wang P, Stroop D. Sex hormone-binding globulin, oligomenorrhea, polycystic ovary syndrome, and childhood insulin at age 14 years predict metabolic syndrome and class III obesity at age 24 years. J Pediatr 2011;159:308–313.e2. http://dx.doi.org/10.1016/j.jpeds.2011.01.018.

[5] Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes. JAMA 2006;295:1288. http://dx.doi.org/10.1001/jama.295.11.1288.

[6] Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2011;40:189–207. http://dx.doi.org/10.1093/ije/dyq158.

[7] Brand JS, Rovers MM, Yeap BB, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PLoS One 2014;9:e100409. http://dx.doi.org/10.1371/journal.pone.0100409.

[8] Nielsen J, Jensen RB, Juul A. Increased sex hormone-binding globulin levels in children and adolescents with thyrotoxicosis. Horm Res Paediatr 2013;79:157–61. http://dx.doi.org/10.1159/000348837.

[9] Vermeulen A, Andó S, Verdonck L. Prolactinomas, testosterone-binding globulin, and androgen metabolism. J Clin Endocrinol Metab 1982;54:409–12. http://dx.doi.org/10.1210/jcem-54-2-409.

[10] Maruyama Y, Adachi Y, Aoki N, Suzuki Y, Shinohara H, Yamamoto T. Mechanism of feminization in male patients with non-alcoholic liver cirrhosis: role of sex hormone-binding globulin. Gastroenterol Jpn 1991;26:435–9.

[11] Nguyen HV, Mollison LC, Taylor TW, Chubb SAP, Yeap BB. Chronic hepatitis C infection and sex hormone levels: effect of disease severity and recombinant interferon-alpha therapy. Intern Med J 2006;36:362–6. http://dx.doi.org/10.1111/j.1445-5994.2006.01093.x.

[12] Antonio L, Wu FCW, O'Neill TW, et al. Associations between sex steroids and the development of metabolic syndrome: a longitudinal study in European men. J Clin Endocrinol Metab 2015;100:1396–404. http://dx.doi.org/10.1210/jc.2014-4184.

[13] Chubb SAP, Hyde Z, Almeida OP, et al. Lower sex hormone-binding globulin is more strongly associated with metabolic syndrome than lower total testosterone in older men: the Health in Men Study. Eur J Endocrinol 2008;158:785–92. http://dx.doi.org/10.1530/EJE-07-0893.

[14] Ukkola O, Gagnon J, Rankinen T, et al. Age, body mass index, race and other determinants of steroid hormone variability: the HERITAGE Family Study. Eur J Endocrinol 2001;145:1–9.

[15] Kupelian V, Shabsigh R, Travison TG, Page ST, Araujo AB, McKinlay JB. Is there a relationship between sex hormones and erectile dysfunction? Results from the Massachusetts Male Aging Study. J Urol 2006;176:2584–8. http://dx.doi.org/10.1016/j.juro.2006.08.020.

[16] Laurent MR, Hammond GL, Blokland M, et al. Sex hormone-binding globulin regulation of androgen bioactivity in vivo: validation of the free hormone hypothesis. Sci Rep 2016;6:35539. http://dx.doi.org/10.1038/srep35539.

[17] Vos MJ, Mijnhout GS, Rondeel JMM, Baron W, Groeneveld PHP. Sex hormone binding globulin deficiency due to a homozygous missense mutation. J Clin Endocrinol Metab 2014;99:E1798–802. http://dx.doi.org/10.1210/jc.2014-2055.

[18] Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35. http://dx.doi.org/10.1056/NEJMoa0911101.

[19] Jaspers L, Dhana K, Muka T, et al. Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: the Rotterdam Study. J Clin Endocrinol Metab 2016;101:2844–52. http://dx.doi.org/10.1210/jc.2016-1435.

[20] Li J-H, Yu X-H, Zheng J-B, et al. The reproductive health indices and sex hormone levels in middle-aged and elderly Chinese men. Aging Male 2016;19:143–7. http://dx.doi.org/10.1080/13685538.2016.1188068.

[21] Travison TG, O'Donnell CJ, Bhasin S, et al. Circulating sex steroids and vascular calcification in community-dwelling men: the Framingham Heart Study. J Clin Endocrinol Metab 2016;101:2160–7. http://dx.doi.org/10.1210/jc.2015-4299.

[22] Kische H, Ewert R, Fietze I, et al. Sex hormones and sleep in men and women from the general population: a cross-sectional observational study. J Clin Endocrinol Metab 2016;101:3968–77. http://dx.doi.org/10.1210/jc.2016-1832.

[23] Jensen TK, Finne KF, Skakkebæk NE, et al. Self-reported onset of puberty and subsequent semen quality and reproductive hormones in healthy young men. Hum Reprod 2016;31:1886–94. http://dx.doi.org/10.1093/humrep/dew122.

[24] Woods GN, Huang M-H, Cawthon PM, et al. SHBG, sex steroids, and kyphosis in older men: the MrOS study. J Bone Miner Res 2016;31:2123–8. http://dx.doi.org/10.1002/jbmr.2901.

[25] Shen X, Wang R, Yu N, et al. Reference ranges and association of age and lifestyle characteristics with testosterone, sex hormone binding globulin, and luteinizing hormoneamong 1166 Western Chinese men. PLoS One 2016;11:e0164116. http://dx.doi.org/10.1371/journal.pone.0164116.

[26] Orwoll ES, Lapidus J, Wang PY, et al. The limited clinical utility of testosterone, estradiol, and sex hormone binding globulin measurements in the prediction of fracture risk and bone loss in older men. J Bone Miner Res 2017;32(March (3)):633–40.

[27] Antonio L, Wu FCW, O'Neill TW, et al. Associations between sex steroids and the development of metabolic syndrome: a longitudinal study in European men. J Clin Endocrinol Metab 2015;100:1396–404. http://dx.doi.org/10.1210/jc.2014-4184.

[28] Hsu B, Cumming RG, Naganathan V, et al. Associations between circulating reproductive hormones and SHBG and prevalent and incident metabolic syndrome in community-dwelling older men: the Concord Health and Ageing in Men Project. J Clin Endocrinol Metab 2014;99:E2686–91. http://dx.doi.org/10.1210/jc.2014-2464.

[29] Macdonald AA, Stewart AW, Farquhar CM. Body mass index in relation to semen quality and reproductive hormones in New Zealand men: a cross-sectional study in fertility clinics. Hum Reprod 2013;28:3178–87. http://dx.doi.org/10.1093/humrep/det379.

[30] Haring R, Völzke H, Spielhagen C, Nauck M, Wallaschofski H. The role of sex hormone-binding globulin and testosterone in the risk of incident metabolic syndrome. Eur J Prev Cardiol 2013;20:1061–8. http://dx.doi.org/10.1177/2047487312452965.

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[31] Milewicz A, Krzyżanowska-Świniarska B, Miazgowski T, et al. The reference values of sex hormones and SHBG serum levels in subjects over 65 years old—The PolSenior Study. Endokrynol Pol 2013;64:82–93.

[32] Maggio M, Cattabiani C, Lauretani F, et al. SHBG and endothelial function in older subjects. Int J Cardiol 2013;168:2825–30. http://dx.doi.org/10.1016/j.ijcard.2013.03.083.

[33] RY-T Chen, Ng K-K. Self-referred older Asian males in a men's health clinic: the inter-relationships between androgens, metabolic parameters and quality of life measures. Aging Male 2010;13: 233–41. http://dx.doi.org/10.3109/13685538.2010.487550.

[34] Stefan N, Schick F, Häring H-U. Sex hormone-binding globulin and risk of type 2 diabetes. N Engl J Med 2009;361:2675–6. http://dx.doi.org/10.1056/NEJMc0910143.

[35] Corona G, Mannucci E, Fisher AD, et al. Low levels of androgens in men with erectile dysfunction and obesity. J Sex Med 2008;5:2454–63. http://dx.doi.org/10.1111/j.1743-6109.2008.00856.x.

[36] Emmelot-Vonk MH, Verhaar HJJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA 2008;299:39–52. http://dx.doi.org/10.1001/jama.2007.51.

[37] Goncharov NP, Katsya GV, Chagina NA, Gooren LJ. Three definitions of metabolic syndrome applied to a sample of young obese men and their relation with plasma testosterone. Aging Male 2008;11:118–22. http://dx.doi.org/10.1080/13685530802204629.

[38] Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. Eur J Endocrinol 2006;155:443–52. http://dx.doi.org/10.1530/eje.1.02241.

[39] Gannagé-Yared M-H, Fares F, Semaan M, Khalife S, Jambart S. Circulating osteoprotegerin is correlated with lipid profile, insulin sensitivity, adiponectin and sex steroids in an ageing male population. Clin Endocrinol 2006;64:652–8. http://dx.doi.org/10.1111/j.1365-2265.2006.02522.x.

[40] Muller M, Grobbee DE, Tonkelaar den I, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab 2005;90:2618–23. http://dx.doi.org/10.1210/jc.2004-1158.

[41] Nuver J, Smit AJ, Wolffenbuttel BHR, et al. The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol 2005;23:3718–25. http://dx.doi.org/10.1200/JCO.2005.02.176.

[42] Undén A-L, Elofsson S, Brismar K. Gender differences in the relation of insulin-like growth factor binding protein-1 to cardiovascular risk factors: a population-based study. Clin Endocrinol 2005;63:94–102. http://dx.doi.org/10.1111/j.1365-2265.2005.02306.x.

[43] Tong PCY, Ho C-S, Yeung VTF, et al. Association of testosterone, insulin-like growth factor-I, and C-reactive protein with metabolic syndrome in Chinese middle-aged men with a family history of type 2 diabetes. J Clin Endocrinol Metab 2005;90:6418–23. http://dx.doi.org/10.1210/jc.2005-0228.

[44] Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 2004;13:1646–50.

[45] Hautanen A. Synthesis and regulation of sex hormone-binding globulin in obesity. Int J Obes Relat Metab Disord 2000;24(Suppl 2):S64–70.

[46] Phillips GB. Relationship between serum sex hormones and the glucose-insulin-lipid defect in men with obesity. Metab Clin Exp 1993;42:116–20.

[47] Onat A, Hergenç G, Karabulut A, Albayrak S, Can G, Kaya Z. Serum sex hormone-binding globulin, a determinant of cardiometabolic disorders independent of abdominal obesity and insulin resistance in elderly men and women. Metabolism 2007;56(October (10)):1356–62.

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