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INFLUENCE OF SEX HORMONE-BINDING GLOBULIN (SHBG) ON THE LEVEL OF FREE TESTOSTERONE FRACTION IN OLDER OVERWEIGHT MEN

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Abstract

Relevance. Serum SHBG concentration varies across different stages of a man's life. In individuals with excess body weight and visceral obesity, SHBG levels may decrease, which in turn disrupts the balance between bound and free testosterone. This may lead to functional hypogonadism, particularly in middle-aged and older men. However, the mechanisms and the extent of SHBG influence on free testosterone levels in the context of excess body weight remain a subject of scientific debate.

Study objective. To assess the effect of sex hormone-binding globulin (SHBG) on the level of free testosterone fraction in men with excess body weight.

Materials and methods. The study involved 326 men living in Semey, Abay region. The subjects were stratified by body mass index (BMI) and divided into two groups: the study group (112 overweight men, BMI 25-29.9 kg/m²) and the control group (214 normal-weight men, BMI <25 kg/m²).

Results. Sex hormone-binding globulin (SHBG) levels were negatively correlated with body mass index, rs = -0.218. Free testosterone showed no differences between the normal-weight and overweight groups. A significant correlation was found between SHBG and free testosterone (rs = -0.422, $p < 0.01$). This confirms the role of SHBG in regulating free testosterone levels in the blood.

Discussion. With excess weight, SHBG levels in the blood decrease, which then has a cascading effect on the distribution of testosterone between its bound and free fractions. A significant correlation between SHBG and free testosterone has been proven. SHBG plays a key role in the binding and transport of sex hormones.

Conclusions. A significant correlation between SHBG and free testosterone has been demonstrated. In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation.

Keywords: *sex hormone-binding globulin (SHBG), free testosterone fraction, older men, overweight.*

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Резюме

ВЛИЯНИЕ ГЛОБУЛИНА, СВЯЗЫВАЮЩЕГО ПОЛОВЫЕ ГОРМОНЫ (ГСПГ), НА УРОВЕНЬ СВОБОДНОЙ ФРАКЦИИ ТЕСТОСТЕРОНА У МУЖЧИН СТАРШЕГО ВОЗРАСТА С ИЗБЫТОЧНЫМ ВЕСОМ

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Актуальность. Концентрация ГСПГ в сыворотке меняется в разные возрастные периоды жизни мужчины. При избыточной массе тела и висцеральном ожирении уровень ГСПГ может снижаться, что, в свою очередь, нарушает соотношение между связанным и свободным тестостероном. Это может приводить к состоянию функционального гипогонадизма, особенно у мужчин среднего и пожилого возраста. Однако механизмы и степень влияния ГСПГ на уровень свободного тестостерона при избыточной массе тела остаются предметом научной дискуссии.

Цель исследования. Влияние глобулина связывающего гормона (ГСПГ) на уровень свободной фракции тестостерона у мужчин на фоне избыточного веса.

Материалы и методы. В исследовании приняло участие 326 мужчин проживающие в городе Семей, области Абай. Обследованные стратифицированы по ИМТ и распределены на 2 группы: основная группа- с избыточной массой тела- 112 мужчин (ИМТ от 25- 29,9 кг/м^2) и контрольная группа с нормальным - 214 мужчин (ИМТ до 25 кг/м^2).

Результаты. Уровень глобулина, связывающего половые гормоны (ГСПГ), отрицательно коррелирует с индексом массы тела, r_s= -0,218. Свободный тестостерон не показал различий между группами с нормальным и избыточным весом. Установлено наличие значимой корреляционной связи между ГСПГ и свободным тестостероном (r_s = -0,422, p < 0,01). Это подтверждает роль ГСПГ в регулировании уровня свободного тестостерона в крови.

Обсуждение. При избыточном весе уровень ГСПГ в крови снижается. Это оказывает каскадное влияние на распределение тестостерона между его связанными и свободными фракциями. Доказана значимая корреляционная связь между ГСПГ и свободным тестостероном. ГСПГ играет ключевую роль в связывании и транспорте половых гормонов.

Выводы. Доказана значимая корреляционная связь между ГСПГ и свободным тестостероном. У мужчин старших возрастных групп эректильная функция определяется не только уровнем свободного тестостерона, но и состоянием сосудистой, эндотелиальной, нервной и метаболической регуляции.

Ключевые слова. *глобулин связывающий половые гормоны (ГСПГ), фракция свободного тестостерона, мужчины старшего возраста, избыточный вес.*

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Түйіндеме

АРТЫҚ ДЕНЕ САЛМАҒЫ БАР ЕГДЕ ЖАСТАҒЫ ЕР АДАМДАРДА ЖЫНЫС ГОРМОНДАРЫН БАЙЛАНЫСТЫРАТЫН ГЛОБУЛИННІҢ (ЖГБГ) ТЕСТОСТЕРОННЫҢ БОС ФРАКЦИЯСЫ ДЕҢГЕЙІНЕ ӘСЕРІ

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Өзектілігі. Ер адамдардың өмірінің әртүрлі жас кезеңдерінде қан сарысуындағы жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) концентрациясы өзгереді. Артық дене салмағы мен висцералды семіздік жағдайында ЖГБГ деңгейінің төмендеуі байқалуы мүмкін, бұл өз кезегінде байланысқан және бос тестостерон арасындағы арақатынастың бұзылуына әкеледі. Аталған өзгерістер, әсіресе орта және егде жастағы ер адамдарда, функционалдық гипогонадизмнің дамуына себеп болуы ықтимал. Алайда артық дене салмағы жағдайында ЖГБГ-ның бос тестостерон деңгейіне әсер ету механизмдері мен оның ықпал ету дәрежесі әлі күнге дейін ғылыми талқылау нысаны болып отыр.

Зерттеу мақсаты. Артық дене салмағы бар ер адамдарда жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) тестостеронның бос фракциясының деңгейіне әсерін бағалау.

Материалдар мен әдістер. Зерттеуге Абай облысы, Семей қаласында тұратын 326 ер адам қатысты. Зерттелушілер дене салмағының индексі (ДСИ) бойынша стратификацияланып, екі топқа бөлінді: негізгі топ —

артық дене салмағы бар 112 ер адам (ДСИ 25–29,9 кг/м²) және бақылау тобы — дене салмағы қалыпты 214 ер адам (ДСИ ≤25 кг/м²).

Нәтижелер. Жыныс гормондарын байланыстыратын глобулин (ЖГБГ) деңгейі дене салмағының индексімен теріс корреляция көрсетті (rs = −0,218). Қалыпты және артық салмақты топтар арасында бос тестостерон деңгейі бойынша айтарлықтай айырмашылық анықталған жоқ. Сонымен қатар ЖГБГ мен бос тестостерон арасында статистикалық мәнді корреляциялық байланыс анықталды (rs = −0,422, p < 0,01), бұл ЖГБГ-ның қандағы бос тестостерон деңгейін реттеудегі рөлін дәлелдейді.

Талқылау. Артық дене салмағы жағдайында қандағы ЖГБГ деңгейі төмендейді, бұл тестостеронның байланысқан және бос фракциялары арасындағы таралуына каскадты әсер етеді. ЖГБГ мен бос тестостерон арасында мәнді корреляциялық байланыс бар екені дәлелденді. ЖГБГ жыныс гормондарын байланыстыру мен тасымалдауда негізгі рөл атқарады.

Қорытындылар. ЖГБГ мен бос тестостерон арасында статистикалық мәнді корреляциялық байланыс анықталды. Егде жастағы ер адамдарда эректильді функция тек бос тестостерон деңгейімен ғана емес, сонымен қатар тамырлық, эндотелиалдық, жүйкелік және метаболикалық реттелу жағдайымен де анықталады.

Түйінді сөздер: *жыныс гормондарын байланыстыратын глобулин (ЖГБГ), бос тестостерон фракциясы, егде жастағы ер адамдар, артық дене салмағы.*

Дәйексөз үшін:

Аккалиев М.Н., Масабаева М.Р., Қазанғапов Р.С., Рахыжанова С.О., Апсаликов Б.А., Жунуспекова А., Базарбеков Р.Ж., Бухариева С.С. Артық дене салмағы бар егде жастағы ер адамдарда жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) тестостеронның бос фракциясы деңгейіне әсері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 14-20. *doi 10.34689/SH.2025.27.6.002*

Introduction

In recent decades, there has been a steady increase in the prevalence of overweight and obesity, which represents a serious medical and social problem worldwide. According to the World Health Organization (WHO), more than half of the adult male population in both developed and developing countries is overweight [1]. In the presence of excess body weight, a significant proportion of men experience hormonal imbalance and reduced androgen levels.

Androgen deficiency is determined by serum testosterone levels. In the circulation, testosterone exists in three fractions: free (approximately 2%), not bound to transport proteins; weakly bound (about 38%), reversibly associated with albumin; and bound (around 60%), tightly bound to sex hormone–binding globulin (SHBG) [2]. The free fraction of testosterone (approximately 1–3% of the total level) is considered biologically active and exerts a direct physiological effect on target tissues. The concentration of androgens in the blood depends not only on their rate of synthesis but also on the efficiency of their transport to target cells. The primary transport protein for androgens is SHBG [3]. SHBG is synthesized in the liver and serves as the primary transport protein for hydrophobic androgens in the bloodstream. It plays an important role in regulating the bioavailability of all androgen fractions [4].

The serum concentration of SHBG changes across different age periods in men. With increasing chronological age, SHBG levels rise while the total testosterone concentration remains within the normal range. This leads to a decrease in free testosterone. Changes in BMI and the accumulation of adipose tissue also alter SHBG concentrations [5]. There is substantial evidence indicating that excess body weight, particularly visceral obesity, is associated with reduced SHBG concentrations, leading to alterations in the equilibrium between bound and free testosterone [6]. This may lead to a state of functional hypogonadism, particularly in middle-aged and older men. However, the mechanisms and extent of SHBG's influence on free testosterone levels in individuals with excess body weight remain a subject of scientific debate.

In this context, studying the relationship between SHBG concentration and free testosterone levels in men with excess body weight is highly relevant. The results obtained may contribute to more accurate diagnosis of androgen deficiency and inform the selection of strategies for hormonal correction in this patient population.

Study Objective: To evaluate the influence of sex hormone-binding globulin (SHBG) on the level of free testosterone fraction in men with excess body weight.

2. Materials and Methods

The study included 326 men residing in the city of Semey, Abay region. Participants were randomly selected from patients who presented to a urologist, aged 45 to 65 years, and had excess body weight. All participants provided informed consent to take part in the study.

The subjects were stratified by BMI and divided into two groups: the main group—overweight men with a BMI of 25–29.9 kg/m² (n = 112), and the control group with normal BMI below 25 kg/m² (n = 214).

Inclusion criteria:

- Male sex only;
- Overweight status (BMI ranging from 25.0 to 29.9 kg/m²);
- Age between 45 and 65 years;
- Written informed consent to participate in the study.

Exclusion criteria:

- BMI < 24.9 kg/m²;
- Age younger than 45 years;
- Presence of acute psychiatric conditions;
- Presence of acute infectious diseases;
- Presence of decompensated somatic diseases;
- Withdrawal from the study before completion of statistical analysis.

Body mass index (BMI) was calculated as the ratio of body

weight in kilograms to the square of height in meters (BMI = weight [kg] / height² [m²]). Body weight was measured with participants wearing underwear only and without shoes. Waist circumference was measured in the standing position at the level of the umbilicus, directly on the skin.

Assessment and classification of erectile dysfunction were performed using a questionnaire based on the validated International Index of Erectile Function-5 (IIEF-5). The reference values for the IIEF-5 were as follows: no erectile dysfunction (normal, 21–25 points); mild erectile dysfunction (16–20 points); moderate erectile dysfunction (11–15 points); severe erectile dysfunction (5–10 points).

Ethical approval and informed consent.

Written informed consent was obtained from all participants in accordance with the Declaration of the World Medical Association (Declaration of Helsinki). Participants were provided with information regarding the purpose of the study and the procedures involved. The study protocol was approved by the Ethics Committee of the Semey Medical University (Protocol No. 11, June 23, 2020).

Laboratory assessments.

Biochemical parameters, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and albumin, were measured at the commercial laboratory INVIVO using a Cobas 8000 analyzer (Roche Diagnostics, Switzerland). Reference ranges were as follows: HDL- 0.78–2.20 mM/L; LDL- 2.33–5.31 mM/L; triglycerides- 1.70–2.25 mM/L; and albumin- 35–55 g/L.

Total testosterone, sex hormone–binding globulin (SHBG), and luteinizing hormone (LH) levels were also determined at the commercial laboratory INVIVO using an Architect i2000SR analyzer (Abbott Laboratories, IL, USA). Reference ranges were as follows: SHBG- 10–57 nM/L; LH- 1.14–8.75 mIU/mL; total testosterone- 5.41–19.54 nM/L.

Free and bioavailable testosterone fractions were calculated using an online calculator (https://www.issam.ch/freetesto.htm) based on total testosterone, SHBG, and albumin concentrations.

Statistical analysis.

Statistical analysis was performed using SPSS software (version 20.0). Both parametric and nonparametric statistical methods were applied. The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Quantitative variables with a normal distribution were expressed as mean ± standard deviation (M ± SD), whereas non-normally distributed variables were presented as median and interquartile range (Me [IQR]). For comparative analysis of quantitative variables, Student's t-test and the Mann–Whitney U- test for independent samples were used. Spearman's rank correlation coefficient (r_s) was applied to evaluate the association between two quantitative variables.

Results.

The average age of participants was 52(12) years in the study group and 58 (12) years in the control group, indicating a statistically relevant age difference, with younger individuals predominating in the study cohort.

Table 1.

Indicators of Androgen and Lipid Profiles.

Parameters	Main group (n=112) from 25–29.9 kg/m²	Control group (n=214) to ≤25 kg/m²	p
Body mass index (BMI)	29,3± 0,9	23,6±1,15	<0,001**
Age	46(12) (34-65)	53(12) (37-65)	<0,001*
Waist circumference	106 (11,50) 81-110	90 (7,0) 93-121	<0,001*
Hip circumference	56 (6,0) 47-61	50 (3,0) 42-56	<0,001*
Index of Erectile Function-5 (IIEF-5 score)	26,4± 2,5	22,7± 4,3	0.2**
sex hormone–binding globulin (SHBG)	23,0 (20,05) 10,80-43,20	34,1 (18,5) 10,80- 82,80	<0,001*
Albumin	43,2 (3,9) 28,70- 51,40	45,0 (4,98) 21,40- 52,40	<0,001*
luteinizing hormone LH	3,8 (1,94) 1,64- 12,03	4,09 (2,42) 1,64- 10,44	0,682*
Total testosterone	9,4 (2,14) 5,01- 12,75	12,5 (3,14) 8,42- 17,40	<0,001*
Bioavailable testosterone	4,99 5,3 (1,89)	5,14 5,3 (1,8)	0,361*
Free testosterone	0,213 0,2 (0,07)	0,210 0,2 (0,09)	0,032*
Triglycerides	2,5 (1,83) 0,53- 10,80	1,7 (1,22) 0,87- 7,44	<0,001*
low-density lipoprotein (LDL)	3,9 (+0,6) 2,0- 5,59	3,2 (+0,6) 2,79- 5,62	<0,001*
high-density lipoprotein (HDL)	1,0 (0,27) 0,62- 9,64	1,2 (0,63) 0,78- 9,05	0,384*

Notes:
1 * – Mann–Whitney U test, Me (IQR) (median (interquartile range)), min and max values;
2 ** – Student's t-test, M ± SD (mean ± standard deviation).

In this context, the higher BMI observed at a younger age may be attributed to the influence of hypogonadism. A consistent pattern was observed: as BMI increased, thigh circumference and body weight also increased. A negative correlation was noted between erectile dysfunction and BMI. An increase in BMI was significantly associated with

greater severity of erectile dysfunction (r_s = −0.560, p < 0.01). Additionally, sex hormone–binding globulin (SHBG) levels demonstrated a significant inverse correlation with BMI. The correlation coefficient (r_s) was –0.218, which, at p < 0.01, confirms the statistical significance of this association. As BMI increases, SHBG levels decrease, demonstrating the impact of obesity on the concentration of this protein. This observation directly affects circulating total testosterone concentrations, which are largely modulated by SHBG. A significant positive association was identified between SHBG and total testosterone levels (r_s = 0.266, p < 0.01). Moreover, decreases in serum total testosterone were proportional to SHBG concentrations, supporting the established role of SHBG as the principal carrier protein for sex steroids and a key regulator of their bioavailability and biological effects. These results confirm the importance of SHBG in regulating testosterone levels and underline its essential role in maintaining hormonal balance. In a comparative analysis with the normal-weight group, albumin levels were noticeably lower in the overweight group. However, no significant differences in albumin levels were observed when compared with other biochemical parameters between the groups. This may indicate that the decrease in albumin in the overweight group did not exert a meaningful influence on the other examined variables. Additionally, luteinizing hormone levels were lower in the overweight group, but still within the reference range. This suggests that excess body weight in this population does not lead to pronounced changes in LH secretion.

Free testosterone did not differ between the normal-weight and overweight groups. This phenomenon is likely associated with the compensatory decrease in total testosterone and SHBG levels in the overweight group, which may influence the balance between bound and free testosterone fractions. Nevertheless, a statistically significant inverse relationship was observed between SHBG and free testosterone (r_s = −0.422, p < 0.01), further substantiating the role of SHBG in the regulation of circulating free testosterone levels. Biologically active testosterone was also lower in the overweight group. This may be explained by the reduction in albumin levels in this group, which disrupts testosterone transport and leads to a decrease in the concentration of the active hormone fraction. The statistical significance of this association was r_s = 0.196 (p < 0.01), confirming the importance of albumin in maintaining biologically active testosterone levels.

Analysis of lipid metabolism revealed that overweight individuals exhibited elevated triglyceride and LDL concentrations, which were inversely related to reductions in SHBG levels. A statistically significant inverse correlation was observed between LDL cholesterol and SHBG (r_s = −0.197, p < 0.001). HDL levels decreased in parallel with SHBG in the overweight group, although this change did not reach statistical significance.

Discussion

The present study focuses on investigating the association between sex hormone–binding globulin (SHBG) levels and the concentration of free testosterone in overweight men. Free testosterone represents the biologically active component of circulating testosterone, existing independently of transport proteins and constituting approximately 1–3% of total serum testosterone [7]. Its concentration depends on the level of total testosterone as well as on the content of binding proteins, primarily sex hormone-binding globulin (SHBG) and, to a lesser extent, albumin. In the present study, a significant association was identified between SHBG levels and indicators of androgen status. Our findings demonstrated that SHBG levels negatively correlate with body mass index (BMI) (r_s = –0.218, p < 0.01). These findings suggest a trend toward reduced SHBG levels in men with excess body weight. The underlying mechanism of this association is likely related to metabolic alterations accompanying overweight, as increased visceral adiposity is associated with hyperinsulinemia due to insulin resistance, as well as elevated leptin concentrations. These inflammatory factors suppress the hepatic synthesis of SHBG[8]. As a result, the level of SHBG in the blood decreases, which produces a cascade effect on the distribution of testosterone between its bound and free fractions. Since SHBG plays a key role in the binding and transport of sex steroids, a reduction in its concentration may directly influence circulating total testosterone levels. In our study, a positive correlation between SHBG and total testosterone was observed (r_s = 0.266, p < 0.01). Men with lower SHBG levels demonstrated reduced total testosterone. This finding supports the assumption that SHBG serves as a major regulator of androgen bioavailability. A decrease in SHBG leads to a reduction in the proportion of testosterone in the bound state, which increases the relative amount of free testosterone. This explains why, in men with excess body weight, moderate reductions in total testosterone may still be accompanied by free testosterone levels within the normal range, owing to decreased SHBG binding. Thus, a compensatory redistribution of testosterone fractions occurs, allowing the biological activity of androgens to be maintained even when total testosterone levels decline.

In cases of pronounced obesity accompanied by a reduction in albumin levels, the concentration of biologically active testosterone (the sum of free and albumin-bound testosterone) may also decrease. This occurs because a portion of testosterone previously bound to albumin shifts into the free fraction. However, overall androgen activity may decline due to reduced total testosterone levels and gonadal dysfunction [9].

Excess body weight has a significant impact on lipid metabolism and hormonal status. In the presence of obesity, insulin resistance and inflammatory processes develop, adversely affecting lipid metabolism. This leads to an increase in triglyceride and LDL levels. The concentration of high-density lipoproteins (HDL) also decreases. These metabolic changes are associated with reduced hepatic synthesis of sex hormone–binding globulin (SHBG) [10].

Age-associated reductions in total testosterone activate compensatory feedback pathways, resulting in elevated luteinizing hormone (LH) secretion. Circulating LH levels may therefore serve as an indicator of gonadal functional integrity. Our findings demonstrate that this regulatory response is preserved in men with normal body mass. In contrast, individuals with excess body weight exhibit a decline in LH concentrations. This phenomenon is likely related to enhanced aromatase activity within adipose tissue, which promotes the conversion of testosterone to

estradiol. Increased estradiol levels exert negative feedback on LH secretion and inhibit the release of gonadotropin-releasing hormone (GnRH). [11]. As a result, circulating testosterone levels decline. In our study, the concentration of free testosterone was similar in both groups. However, despite the absence of significant differences in measured hormonal levels, the overweight group demonstrated a pronounced pattern of erectile dysfunction.

In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation [12]. In visceral obesity, a number of pathophysiological disturbances develop, which can lead to erectile dysfunction even if free testosterone levels remain within the normal range.

In the presence of excess adipose tissue, insulin resistance and elevated levels of free fatty acids are observed. These factors lead to a reduction in nitric oxide (NO) synthesis by the endothelium of penile vessels. NO deficiency impairs the relaxation of the corpora cavernosa and hinders adequate arterial blood inflow, which is the primary mechanism of erection. In older men, obesity accelerates atherogenesis. Narrowing of arterial lumens and decreased arterial elasticity reduce blood flow to the corpora cavernosa.

Since the penile vessels have a small diameter, erectile dysfunction often represents an early manifestation of systemic atherosclerosis. Insulin resistance also promotes the development of chronic subclinical inflammation, contributing to oxidative stress.

Even at normal levels of free testosterone, these mechanisms impair the hemodynamic phase of erection [13].

These factors lead to decreased libido, impaired psychosexual response, and exacerbation of erectile dysfunction, even though free testosterone levels formally remain within the normal range.

Moreover, reductions in SHBG and free testosterone in men with excess body weight may further exacerbate metabolic disturbances, creating a vicious cycle: hypogonadism increases insulin resistance and promotes fat accumulation, which in turn further decreases androgen levels. These interrelationships are particularly important for men over 40, who already experience a physiological decline in testosterone production.

The clinical relevance of the observed associations is that reliance solely on total testosterone measurements may not adequately reflect androgen status in men with excess body weight. In this population, evaluation of sex hormone–binding globulin (SHBG) concentrations and estimation of free testosterone using validated calculation methods (such as the Vermeulen equation) provide greater diagnostic value.

Accordingly, our findings highlight the importance of an integrated hormonal evaluation in overweight men and support the consideration of SHBG and free testosterone parameters in diagnostic and therapeutic algorithms for disorders of androgen homeostasis. Future prospective studies are needed to evaluate the impact of body weight normalization and metabolic parameter improvement on the dynamics of SHBG and free testosterone levels.

Conclusions

A correlation exists between SHBG and free testosterone. In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation.

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