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# CORRELATION OF SHBG AND TESTOSTERONE FRACTION IN OVERWEIGHT MEN AGAINST THE BACKGROUND OF AGE-RELATED HYPOGONADISM IN MEN OF THE KAZAKH POPULATION

**Resume:** *In total, 417 Kazakh men aged 35 to 65 inhabiting in Semey, East Kazakhstan region, have been involved in the study. The examined patients were stratified by BMI and divided into 2 groups: with overweight BMI from 25 - 29.9 kg/m2 (group 1, n=135) and with normal BMI up to 25 kg/m2 (group 2, n=282).*
*Results. In our study the level of SHBG negatively correlates with the level of BMI Rho (= - 0.218, p<0.01). The higher BMI is, the lower the level of SHBG is. SHBG correlated well with total testosterone Rho (=0.266, P<0.01), consistent with the biological role of SHBG as the major sex hormone binding protein. The level of total testosterone in the blood serum decreased in men in direct proportion to SHBG.*
*The fraction of free testosterone did not differ in both groups, possibly due to a compensatory decrease in total testosterone and SHBG. A correlation was observed between SHBG and free testosterone Rho (= -0.422, p<0.01).*
*Biologically active testosterone was lower in the overweight group. This fact may be explained by a decrease in albumin against the background of overweight. Statistical significance of Rho (=0.196, p<0.01).*
*Conclusion. With excess weight, not only a decrease in the level of SHBG as a depot of testosterone, but also a decrease in testosterone secretion and a bioavailable fraction deficiency cause hypogonadism in older men. The development of insulin resistance with increase in BMI leads to a decrease in SHBG levels.*
**Key words:** *sex hormone-binding hormone (SHBG), testosterone fractions, overweight, age-related hypogonadism.*

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## ҚАЗАҚ ПОПУЛЯЦИЯСЫНДАҒЫ ЖАСҚА БАЙЛАНЫСТЫ ГИПОГОНАДИЗМ АЯСЫНДА АРТЫҚ САЛМАҒЫ БАР ЕРЛЕРДЕГІ ЖЫНЫС ГОРМОНДАРЫН БАЙЛАНЫСТЫРАТЫН ГОРМОН (ЖГБГ) МЕН ТЕСТОСТЕРОН ФРАКЦИЯСЫНЫҢ ӨЗАРА БАЙЛАНЫСЫ

**Мақсаты:** артық салмақ аясында қазақ популяциясының ерлеріндегі ЖГБГ мен тестостерон фракциясының өзара байланысын анықтау.

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## ВЗАИМОСВЯЗЬ ГСПГ И ФРАКЦИИ ТЕСТОСТЕРОНА У МУЖЧИН С ИЗБЫТОЧНЫМ ВЕСОМ НА ФОНЕ ВОЗРАСТНОГО ГИПОГОНАДИЗМА В КАЗАХСКОЙ ПОПУЛЯЦИИ

**Резюме:** Определить взаимосвязь ГСПГ и фракции тестостерона у мужчин казахской популяции на фоне избыточного веса.
**Материалы и методы.** Всего в исследовании приняло участие 417 мужчин казахской национальности в возрасте от 35 до 65

**Материалдар мен әдістер.** Зерттеуге Шығыс Қазақстан облысы, Семей қаласында тұратын 35 жастан 65 жасқа дейінгі қазақ ұлтының 417 ер адамы қатысты. Тексерілген ДМИ бойынша стратификацияланған, 2 топқа бөлінген: артық дене салмағы 25 - 29,9 кг/м2-ден (1-топ, n=135) және қалыпты ДСИ-25 кг/м2-ге дейін (2-топ, n=282).

**Нәтижелер.** Біздің зерттеулерімізде ЖГБГ деңгейі ДСИ Rho деңгейімен теріс корреляциялайды (=- 0,218, p<0,01), ДСИ неғұрлым жоғары болса, ЖГБГ деңгейі соғұрлым төмен болады. ЖГБГ жалпы тестостеронмен жақсы корреляцияланды Rho (=0,266, p <0,01), бұл ЖГБГ жыныстық гормондарды байланыстыратын негізгі ақуыз ретінде биологиялық рөліне сәйкес келеді. Қан сарысуындағы жалпы тестостерон деңгейі ерлерде ЖГБГ-ға тікелей байланысты төмендеді. Еркін тестостерон фракциясының екі топта да айырмашылықтары болмады, мүмкін бұл жалпы тестостерон мен ЖГБГ компенсаторлық төмендеуіне байланысты. ЖГБГ мен еркін тестостерон Rho (= -0,422, p<0,01) арасында корреляциялық байланыс байқалды. Биологиялық белсенді тестостерон артық салмақ тобында төмен болды. Бұл факт артық салмақ аясында альбуминнің төмендеуімен байланысты болуы мүмкін. Rho статистикалық маңыздылығы (=0,196, p<0,01).

**Тұжырымдар.** Артық салмақ болған кезде тестостерон депосы ретінде ЖГБГ деңгейінің төмендеуі ғана емес, сонымен қатар тестостерон секрециясының төмендеуі және биожетімді фракцияның жетіспеушілігі егде жастағы ер адамдарда гипогонадизмнің себептері болып табылады. Инсулиндірезистенттілікті дамыту ИМТ жоғарғы көтерілген кезде ЖГБГ деңгейінің төмендеуіне алып келеді .

**Түйін сөздер:** жыныс гормондарын байланыстыратын гормон (ЖГБГ), тестостерон фракциялары, артық салмақ, жастық гипогонадизм.

лет, проживающие в г. Семей, Восточно-Казахстанской области. Обследованные стратифицированы по ИМТ, распределены на 2 группы: с избыточной массой тела ИМТ от 25 - 29,9 кг/м2 (группа 1, n=135) и с нормальным ИМТ до 25 кг/м2 (группа 2, n=282).

**Результаты.** В нашем исследований уровень ГСПГ отрицательно коррелирует с уровнем ИМТ Rho (= - 0,218, p<0,01), чем выше ИМТ тем ниже уровень ГСПГ. ГСПГ хорошо коррелировал с общим тестостероном Rho ( = 0,266, P <0,01), что согласуется с биологической ролью ГСПГ как основного белка, связывающего половые гормоны. Уровень общего тестостерона в сыворотке крови снижался у мужчин в прямой зависимости от ГСПГ. Фракция свободного тестостерона не имела различий в обеих группах, возможно это связано с компенсаторным снижением общего тестостерона и ГСПГ. Наблюдалась корреляционная связь между ГСПГ и свободным тестостероном Rho (= -0,422, p<0,01).

Биологический активный тестостерон был ниже в группе с избыточным весом. Этот факт возможно объясняется снижением альбумина на фоне избыточного веса. Статистическая значимость Rho (= 0,196, p<0,01).

**Выводы.** При избыточном весе не только снижение уровня ГСПГ как депо тестостерона, но и снижение секреции тестостерона и дефицит биодоступной фракции являются причинами гипогонадизма у мужчин старшего возраста. Развитие инсулинорезистентности при повышений ИМТ ведет к снижению уровня ГСПГ.

**Ключевые слова:** гормон связывающий половые гормоны (ГСПГ), фракции тестостерона, избыточный вес, возрастной гипогонадизм.

**Introduction.** According to the endocrine theory of human aging all morphological and functional changes in organs and tissues occur due to hormone deficiency, among which the deficiency of sex hormones is the most significant [1]. The aging process in men is constantly accompanied by a decrease in testosterone levels [2]. This condition is called age-related hypogonadism. This is a clinical and biochemical syndrome. A decrease in testosterone negatively affects the functions of many organs and systems. The clinical significance of age-related hypogonadism is becoming increasingly relevant, as many countries face the problems of aging society. In particular, more than 60% of the world's population lives in Asia, where there are more than 800 million aging men (over 40 years old), and their number is growing [3,4]. Modern studies prove a direct link between hypogonadism and overweight. Obesity is the main cause aggravating the physiological course of age-related decline in the level of total testosterone and its bioavailable fractions [5].

A specific feature of obesity in men is a change in the metabolism of sex hormones [6], that are one of the factors determining the distribution of fat in the body[7]. In men adipose tissue deposition occurs mainly in the abdominal region and this is the most important risk factor for the development of hormonal and metabolic disorders, which leads to the development of hypogonadism [8,9,10]. With the increasing modernization and urbanization of Asia, most of the future obesity epidemic will be concentrated in the Asian region [11,12]

The most frequently used parameter for the diagnosis of hypogonadism is the measurement of total testosterone and hormone binding sex hormones (SHBG), followed by the calculation of the free and bioavailable fraction of testosterone. However, in the literature there are averaged figures of testosterone and SHBG levels in men in the blood serum, and individual variability complicates timely diagnosis.

This situation is complicated by a number of factors, such as the lack of screening for male hypogonadism in practical healthcare, unavailability of laboratories that determine testosterone fractions. There is no direct correlation between serum testosterone levels and the clinical picture of hypogonadism. The cost and complexity of laboratory determination of the testosterone fraction limits the clinician's ability to make a diagnosis and postpones treatment for a longer period. A change in the concentration

of the SHBG transport protein leads to a decrease in the level of testosterone and its free fraction. This fact allows us to consider SHBG as a marker of age-related men hypogonadism [13,14].

Thus, SHBG should be considered with changes in total or free testosterone to determine the indicators of androgenic status in older men. Traditionally, the level of SHBG is not considered as a risk factor for the development of any diseases (for example, cancer, osteoporosis, heart disease and type 2 diabetes). It is considered as a depot of androgens. The interconnection between testosterone and SHBG against the background of overweight and obesity suggests that SHBG may affect some metabolic processes [15,16,17].

The actual prevalence of overweight and obesity among middle-aged and older men is higher. But this category of people is outside the field of urologists and nutritionists. This is due to the low rate of older men seeking medical attention. A possible reason for the progressive development of complications of the disease in men is unavailability of aesthetic claims to the problem of overweight. Age-related hypogonadism against the background of overweight is a clinical and biochemical syndrome that leads to a significant decrease in the quality of life and adversely affects the function of many systems and organs of the aging body.

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**Aim:** To determine the interconnection of SHBG and testosterone fraction in men of the Kazakh population against the background of overweight.

**Materials and Methods**

*Subjects*

In total, 417 people of Kazakh ethnicity living in Semey, East Kazakhstan region participated in the study, including 135 overweight men and 282 men of the control group with normal weight.

Inclusion criteria:

-male gender;

-age from 35 to 65 years;

-availability of informed consent to participate in the study.

Exclusion criteria:

-presence of severe somatic, oncology, and chronic infectious diseases that have a pronounced negative impact on the state of the body;

-presence of acute disorders of coronary, cerebral, renal circulation in the anamnesis;

-presence of mental illnesses, acute conditions;

-presence of acute infectious diseases of the sexual and non-sexual sphere at the time of the initial examination;

- BMI values below normal weight (<18.5);

- refusal from participation in the study at any stage until the completion of the statistical analysis of the results.

*Ethics approval and consent to participate*

The examined patients were stratified by body mass index (BMI), and divided into 2 groups: with overweight BMI from 25 - 29.9 kg/m2 (group 1, n=135) and with normal BMI up to 25 kg/m2 (group 2, n=282). BMI was calculated by dividing body weight in kilograms by height in square meters. Weighing was carried out in underwear and socks. Waist circumference was measured directly on the skin at the level of the navel in a standing position. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters.

Erectile dysfunction was classified based on the International Index of Erectile Function (IIEF-5) survey, where there is no erectile dysfunction (21-25), mild (16-20), moderate (11-15), severe (5-10)

Informed consent to participate in the study was obtained from all participants in the study in accordance with the Protocol of the Ethical Committee of the Medical University of Semey (No of registration 11) and the requirements of the World Medical Association of Helsinki Declaration.

*Laboratory experiments*

The level of high density lipoproteins (HDL), low density lipoproteins (LDL), triglycerides, albumins in biochemical analyzes was determined by commercial kits obtained from Abbott (Abbott Laboratories, USA) and an Architect C8000 analyzers instrument (Abbott Laboratories, USA). Reference values are HDL (0,78-2,2 mM/L, LDL (2,33-5,31 mM/L), triglycerides (1,7-2,25 mM/L), albumin (35-55 g/L).

General testosterone, sex hormone binding globulin (SHBG) and luteinizing hormone (LH) were tested on Architect i2000SR equipment (Abbott Laboratories, IL, USA) using commercial diagnostic kits (Abbott Laboratories, USA) according to the manufacturer's instruction

Reference values for SHBG, LH and testosterone total are as follows 10-57 nM/L, 1,14-8,75 nM/L, and 5,41-19,54 nM/L correspondingly.

Bioactive и Free testosterone was measured by online calculator http://www.issam.ch/freetesto.htm developed by Hormonology department, University Hospital of Ghent, Belgium, with inputting data for total testosterone, SHBG and albumin.

**Statistics.** Statistical analysis was carried out using the computer program SPSS (version 20.0). The research materials were statistically processed using the methods of parametric and nonparametric analysis. With a normal distribution of variables, the Kolmogorov-Smirnov test was applied. With a normal distribution quantitative variables are represented by average values and their standard deviations (M+SD), while with an abnormal one - in the form of median and interquartile range (Me(IQR)). In descriptive statistics, when comparing quantitative variables, the Student's t-test and the Mann–Whitney U–test

were used for independent samples.
Spearman correlation analysis (Rho) was used to determine the correlation between the two quantitative indicators.

**Results**

The average age of the subjects was 46 (12) in the first group, and 53 (12) in the control group. It should be noted that the groups of men differed in age. The average age of men in the main group is younger than the control one. In this case the increase in BMI in a young age is explained by the influence of hypogonadism. During the observations, a decrease in total testosterone and an increase in hip volume and weight were naturally indictated in regard with BMI. The higher the BMI, the more pronounced the problems with erectile dysfunction, with statistical significance (Rho = -0.560, p<0.01).
The level of SHBG negatively correlates with the level of BMI (Rho = - 0.218, p<0.01), the higher the BMI, the lower the level of SHBG, which undoubtedly affects the level of total testosterone. SHBG correlates well with total testosterone (Rho = 0.266, P <0.01). The level of total testosterone in the blood serum decreased in men in direct dependence on SHBG, which was consistent with the biological role of SHBG as the main protein binding sex hormones. Free testosterone had no differences in both groups, likely this was due to a compensatory decrease in total testosterone and SHBG. There was a correlation between SHBG and free testosterone (Rho= -0.422, p<0.01),( Figure 1).
Biologically active testosterone was lower in the overweight group. This fact may be explained by a decrease in albumin against the background of excess weight. Statistical significance (Rho= 0.196, p<0.01).
In the analysis of lipid metabolism in overweight patients, triglycerides and LDL increased inversely proportional to the decrease in SHBG. A statistically significant interconnection between LDL and SHBG was revealed (Rho= -0.197, p<0.001). HDL in parallel with SHBG decreased with excess weight, without statistical significance.

**Table 1** – Group characteristics

| Parameters | Group 1 | Group 2 | p |
|---|---|---|---|
| | From 25- 29,9 kg/м2 | Up to 25 кkg/м2 | |
| Age | 46(12) (34-65) | 53(12) (37-65) | <0,001* |
| BMI | 29,3± 0,9 | 23,6±1,15 | <0,001** |
| Waist size | 106 (11,50)<br>81- 110 | 90(7,0)<br>93- 121 | <0,001* |
| Hip volume | 56 (6,0)<br>47- 61 | 50 (3,0)<br>42- 56 | <0,001* |
| IIEF-5 | 26,4±2,5 | 22,7±4,3 | 0,2** |

Note:
* – U-Mann-Whitney U test, Me(IQR) (median (midspread)), min and max scores;
** – t-Student's test, M+SD (average+ standard deviation)

Table 2 - Indicators of androgen status

| Indicators | Group 1 | Group 2 | p |
|---|---|---|---|
| | from 25-29,9 kg/м2 | Up to 25 kg/м2 | |
| Total testosterone | 9,4 (2,14)<br>5,01- 12,75 | 12,6(3,00)<br>8,42- 18,40 | <0,001* |
| SHPG | 23,0(20,05)<br>10,80- 43,2 | 34,1(18,5)<br>10,80- 82,80 | <0,001* |
| Albumen | 43,2(3,9)<br>28,70- 51,40 | 45(4,98)<br>21,40- 52-40 | 0,001* |
| Luteinizing hormone | 3,8 (1,94)<br>(1,64-12,03) | 4,09 (2,42)<br>(1,64-10,44) | 0,682* |
| Free testosterone (nM/L,) | 0,213<br>0,2(0,07) | 0,21<br>0,2(0,09) | 0,032* |
| Bioactive testosterone (nM/L) | 4,99<br>5,3(1,89) | 5,14<br>5,3(1,8) | 0,361* |

Note:
* – Mann-Whitney U test, Me(IQR) (median (midspread)), min and max scores;

**Discussion**

The clinical picture of androgen deficiency is determined by the level of testosterone. It circulates in the blood in three states: free testosterone (2%, not bound to transport proteins), weakly bound (38%, reversibly bound to albumin) and bound (60%, strongly bound to SHBG).

A feature of SHBG is its high affinity of binding to testosterone. SHBG is a homodimeric glycoprotein, and both of its monomers can bind sex steroids [19]. SHBG is secreted in the liver. It has a high affinity with testosterone and is an important determinant of the distribution of circulating testosterone in the blood [20]. Testosterone has a weak affinity with albumin, which allows it to easily cleave (dissociate) in tissue capillaries and be effectively accessible for biological activity [21]. The fractions of free unbound testosterone and weakly albumin-bound testosterone in circulation exhibit biological activity to target tissues, and these two fractions together have become known as bioavailable testosterone. It is obvious that the concentration of albumin affects the concentration of the fraction of free and bioavailable testosterone.

As a consequence all testosterone that is not associated with SHBG is considered biologically available to tissues, and therefore bioavailable testosterone may be a better marker of testosterone bioactivity than total testosterone [19]. Total testosterone associated with SHBG is not bioavailable to all target tissues and is directly influenced by the concentration of SHBG.

When overweight, a decrease in total testosterone is primarily interpreted as a reflection of an obesity-related decrease in its circulating carrier protein SHBG.

We consider SHBG as a sequester of hormones to control their bioavailability. Therefore, a change in the level of SHBG synthesis can significantly affect the androgenic status. In publications of recent years, there are two opposite statements regarding the level of SHBG in hypogonadism

Thus, with an increase in calendar age, the level of SHBG increases, which leads to a decrease in the free fraction of testosterone, while maintaining the normal level of total testosterone. With obesity, the concentration of SHBG decreases [23]. The results of our study prove the validity of both statements, considering the negative correlation of SHBG with BMI and positive with age. In the first group with an increased BMI, a decrease in the concentration of SHBG was observed (23.0 (20.05)). In the second group with normal BMI, an increase in the level of SHBG was observed (34.1 (18.5)). In both cases, there is a decrease in the concentration of total testosterone (9.4 (2.14) and 11.3 (3.13)).

The mechanism by which obesity is associated with a reduced level of SHBG remains disputable, it is possible to suppress the synthesis of SHBG in the liver by increased concentrations of insulin [24] which indicates the negative effects of high insulin levels on the production of SHBG in the liver. Accordingly, SHBG is a good indicator of metabolic dysregulation and potential hypogonadism [25].

Decrease in the level of SHBG with an increase in BMI may be a predictor of the development of obesity and diabetes mellitus [26] in combination with a decrease in total testosterone.

With weight gain, the concentration of total testosterone and SHBG is largely associated with abdominal obesity and high triglyceride concentrations [15]. Although the exact mechanisms of association remain debatable, it is possible that low testosterone increases lipoprotein lipase activity by inhibiting lipid uptake, which contributes to the accumulation of visceral adipose tissue. The adipose tissue itself, as the endocrine organ, has a complex structure, in which adipocytes exhibit hormonal and metabolic activity. Visceral obesity enhances the delivery of free fatty acids to the liver, leading to a decrease in hepatic insulin clearance and a further increase in the concentration of circulating insulin, which leads to hyperinsulinemia [27]. Free fatty acids lead to increased synthesis and secretion of small lipoprotein particles of very low density. At the same time, an increase in the level of very low-density lipoproteins leads to clinical hypertriglyceridem

Our research revealed an inverse correlation between low levels of SHBG and high levels of triglycerides and LDL, and a direct relationship with HDL levels.

We are unaware of whether SHBG is just a marker of dysmetabolism or it plays a causal role in the pathophysiology of metabolic disorders such as diabetes and metabolic syndrome.

These observations confirm the need to measure SHBG in the clinical evaluation of men with suspected hypogonadism against the background of overweight and obesity. The age-related decrease in total testosterone, according to the feedback mechanism, leads to an increase in luteinizing hormone. The LH level can provide information about the functional status of the gonads. Our data show that this theory works in men with normal weight. In the presence of excess weight, there is a decrease in luteinizing hormone. The aromatase activity of excess adipose tissue converts testosterone into estradiol. Estradiol has a depressing effect on LH and inhibits the secretion of gonadotropin releasing hormone [29]. Ultimately, this is manifested by a decrease in the level of testosterone in the blood [30].

Summarizing the results of our study, we state that SHBG value is underestimated by urologists in the treatment of older men with hypogonadism against the background of overweight. The values of SHBG can be diametrically opposite. In older men with normal weight the concentration of SHBG increases, while in men with obesity it decreases. When interpreting the results, it is impossible to exclude the factor of polymorphism of the SHBG protein, which even at normal concentrations may be functionally untenable. Not only a decrease in the level of SHBG as a depot of testosterone, but also a decrease in testosterone secretion and a deficiency of the bioavailable fraction can cause hypogonadism in older men. Most formulas for calculating the bioavailable fraction of testosterone

have errors, which should be taken into account by clinicians when diagnosing age-related hypogonadism. In addition, the calculation method does not take into account the rate of dissociation of testosterone from the connection with albumin, as well as the sensitivity of androgen receptors. Reliable analyses are not always available to practicing clinicians, given the complexity of their implementation and high cost. Although the calculated figures for free testosterone are not supported with solid biological basis, they are quite suitable for applying in andrological practice.

Therefore, the procedures of informed clinical decisions require algorithms based on available laboratory methods and clinical manifestations of hypogonadism. Taking into accout the fact that testosterone deficiency itself in older men can occur under the guise of many somatic diseases, such steps will reduce the risk of misclassification of the disease and optimize clinical decision-making in the treatment of androgen disorders in older men against the background of overweight and obesity.

**Conclusion.** When overweight, a decrease in the level of SHBG as a depot of testosterone, and in testosterone

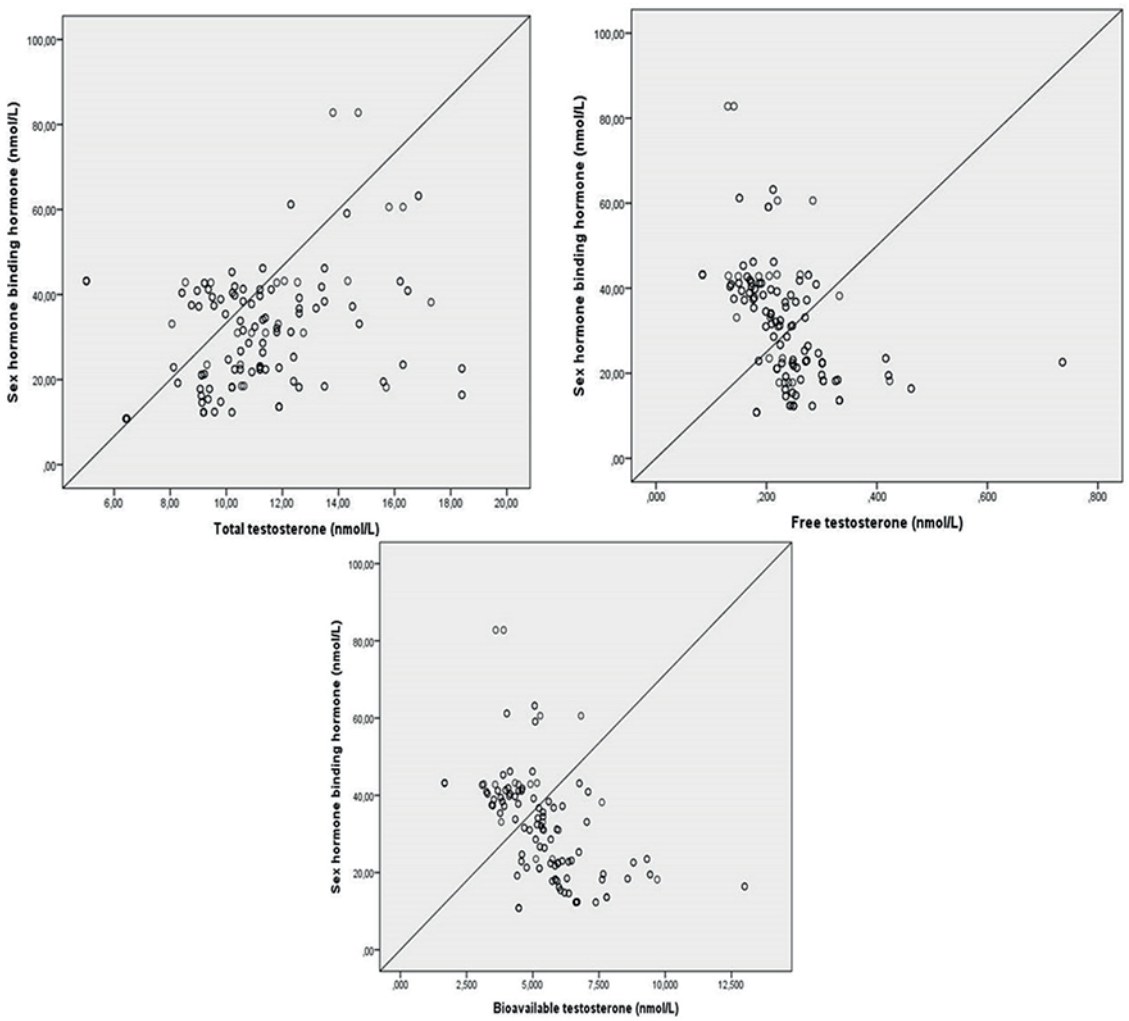


**Figure 1** - Graphs of the correlation of SHBG and testosterone fraction. A: SHBG and total testosterone. B: SHBG and free testosterone. C: SHBG and bioavailable testosterone

**Table 3** - Lipid Metabolism Indicators

| Indicators | Group 1 | Group 2 | p |
|---|---|---|---|
| | From 25- 29,9 kg/м2 | Up to 25 kg/м2 | |
| Triglycerides | 2,5(1,83)<br>0,53- 10,80 | 1,7(1,22)<br>0,87- 7,44 | <0,001* |
| LDL | 3,9(±0,6)<br>2,0- 5,59 | 3,2(±0,6)<br>2,79- 5,62 | <0,001** |
| HDL | 1,0(0,27)<br>0,62- 9,64 | 1,2(0,63)<br>0,78- 9,05 | 0,384* |

secretion, as well a bioavailable fraction deficiency causes hypogonadism in older men. A decrease in the level of SHBG is associated with the development of insulin resistance in overweight. The calculated figures of free testosterone, in spite of having no solid biological basis, might be applicable in andrological practice.

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