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THE RELATIONSHIP BETWEEN TYPES OF OBESITY AND TESTOSTERONE LEVELS IN MEN WITH AGE-RELATED HYPOGONADISM FROM KAZAKH POPULATION

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Abstract

Introduction. Overweight and obesity are stated to be pressing clinical and social health problems around the world. This is a complex disease that develops as a result of genetic factors and environmental factors. At the same time, an important feature of obesity in men is a change in the metabolism of sex hormones. 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 negatively affects the function of many systems and organs of an aging organism.

The study under consideration is aimed at assessing the effect of excess weight on the level of testosterone fraction and lipid metabolism in older men of the Kazakh population. In total, the study included 300 men who underwent a comprehensive clinical examination to determine the presence of hypogonadism. The surveyed were stratified by BMI, and divided into 3 groups: with a normal BMI up to 25 kg / m2 (group 1, n = 145), with an overweight BMI from 25-29.9 kg / m2 (group 2, n = 70) and with obesity BMI from 30 kg / m2 and more (group 3, n = 85).

Results. Total testosterone levels are directly related to SHBG concentration, so changes in blood SHBG levels affect plasma distribution of testosterone and its availability to target tissues and cells. In our studies, the percentage of free testosterone correlated negatively with total testosterone, SHBG, and BMI. But by the outcomes of the study, the calculated free testosterone was stated higher in groups with high BMI. But the reference value of free testosterone according to the literature data was directly proportional to the level of total testosterone and BMI. Our study has revealed a direct correlation between BMI and triglyceride and LDL levels, and an inverse relationship with HDL levels.

Conclusion. Overweight and obesity are accompanied by a decrease in SHBG and total testosterone levels and their decrease correlates to obesity degree. Although the calculated free testosterone do not have a solid biological basis, they are entirely suitable to be applied in andrological practice. Lipid metabolism disorders are more often caused by lifestyle and ethnic food habits.

Key words: *men of the kazakh population, age-related hypogonadism, obesity, testosterone.*

Резюме

ВЗАИМОСВЯЗЬ ВИДОВ ОЖИРЕНИЯ И УРОВНЯ ТЕСТОСТЕРОНА У МУЖЧИН С ВОЗРАСТНЫМ ГИПОГОНАДИЗМОМ В КАЗАХСКОЙ ПОПУЛЯЦИИ

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Введение. Избыточный вес и ожирение являются актуальной клинической и общественной проблемами для здоровья во всем мире. Это комплексное мультифакториальное заболевание, которое развивается вследствие действия генетических факторов и факторов внешней среды. При этом важной особенностью ожирения у мужчин является изменение метаболизма половых гормонов. Возрастной гипогонадизм на фоне избыточного веса является клиническим и биохимическим синдромом, который приводит к значительному снижению качества жизни и отрицательно влияет на функцию множества систем и органов стареющего организма

Цель исследования. Оценить влияние избыточного веса на уровень фракции тестостерона и липидного обмена у мужчин казахской популяции старшего возраста.

Материалы и методы. Всего в исследование включены 300 мужчин, прошедших комплексное клиническое обследование с определением наличия гипогонадизма. Обследованные стратифицированы по индексу массы тела (ИМТ), распределены на 3 группы: с нормальным ИМТ до 25 кг/м^2 (группа 1, n=145), с избыточной массой тела ИМТ от 25- 29,9 кг/м^2 (группа 2, n=70) и с ожирением ИМТ от 30 кг/м^2 и выше (группа 3, n=85).

Результаты. Уровень общего тестостерона напрямую связан с концентрацией глобулина, связывающего половые гормоны (ГСПГ). Изменение уровней ГСПГ в крови влияет на распределение в плазме тестостерона и доступность его к тканям и клеткам-мишеням. В нашем исследований процентное содержание свободного тестостерона отрицательно коррелировало с общим тестостероном, ГСПГ и ИМТ. Но по результатам исследования расчетный свободный тестостерон оказался выше в группах с высоким ИМТ. Но референсное значение свободного тестостерона соответственно литературным данным было прямо пропорционально уровню общего тестостерона и ИМТ. В нашем исследовании выявлена прямая корреляция между ИМТ и уровнем триглицеридов и ЛПНП, и обратная связь с уровнем ЛПВП.

Выводы. Избыточный вес и ожирение сопровождаются снижением уровня ГСПГ и общего тестостерона и их снижение пропорционально степени ожирения. Расчетные цифры свободного тестостерона хоть и не имеют прочной биологической основы, но вполне пригодны для применения в андрологической практике. Нарушение обмена липидов чаще обусловлено образом жизни и этническими пищевыми привычками.

***Ключевые слова**: мужчины казахской популяции, возрастной гипогонадизм, ожирение, тестостерон.*

Түйіндеме

ҚАЗАҚ ПОПУЛЯЦИЯСЫ ЕРЛЕРІНІҢ ЖАСЫНА БАЙЛАНЫСТЫ ГИПОГОНАДИЗМІ БАР СЕМІЗДІК ТҮРЛЕРІ МЕН ТЕСТОСТЕРОН ДЕҢГЕЙІНІҢ АРАСЫНДАҒЫ БАЙЛАНЫС

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Кіріспе. Артық салмақ пен семіздік-бүкіл әлемдегі денсаулық үшін өзекті клиникалық және әлеуметтік проблемалар. Бұл кешенді мультифакториальное ауру, генетикалық факторлар және сыртқы орта факторларының салдарынан дамиды. Бұл жағдайда ерлердегі семіздіктің маңызды ерекшелігі жыныстық гормондардың метаболизмінің өзгеруі болып табылады. Артық салмақ фонында жасқа байланысты гипогонадизм клиникалық және биохимиялық синдром болып табылады. Бұл өмір сапасының едәуір төмендеуіне әкеледі және қартаю ағзасының көптеген жүйелері мен мүшелерінің жұмысына теріс әсер етеді.

Зерттеу мақсаты. Егде жастағы қазақ популяциясындағы ерлердегі тестостерон фракциясы мен липидтер алмасуының деңгейіне артық салмақтың әсерін бағалау.

Материалдар мен әдістер. Зерттеуге гипогонадизмнің бар-жоғын анықтай отырып, кешенді клиникалық тексеруден өткен 300 ер адам кіреді. Тексерілгендер дене салмағы индексы (ДСИ) бойынша стратификацияланған,

3 топқа бөлінген: қалыпты ДСИ-мен 25 кг / м2 дейін (1-топ, n=145), артық дене салмағымен ДСИ - мен 25-29,9 кг/м2 (2-топ, n=70) және семіздікпен ДСИ-мен 30 кг/м2 және одан жоғары (3-топ, n=85).

Нәтижелері. Жалпы тестостерон деңгейі жыныс гормандарын байланыстырушы глобулин (ЖГБГ) концентрациясына тікелей байланысты. Қандағы жыныс гормандарын байланыстырушы глобулин деңгейінің өзгеруі тестостерон плазмасының таралуына және оның мақсатты тіндер мен жасушаларға қол жетімділігіне әсер етеді. Біздің зерттеулерімізде бос тестостеронның пайызы жалпы тестостеронмен, жыныс гормандарын байланыстырушы глобулин және ДСИ-мен теріс байланысты. Бірақ зерттеу нәтижелері бойынша есептелген еркін тестостерон жоғары ДСИ топтарында жоғары болды. Бірақ әдеби мәліметтерге сәйкес еркін тестостеронның анықтамалық мәні жалпы тестостерон мен ДСИ деңгейіне тікелей пропорционалды болды. Біздің зерттеулерімізде ДСИ мен триглицеридтер, ТТЛП арасындағы тікелей байланыс және ТЖЛП деңгейімен кері байланыс анықталды.

Тұжырымдар. Артық салмақ пен семіздік жыныс гормандарын байланыстырушы глобулин және жалпы тестостерон деңгейінің төмендеуімен және олардың семіздік деңгейіне пропорционалды төмендеуімен бірге жүреді. Бос тестостеронның есептелген көрсеткіштерінің күшті биологиялық негізі болмаса да, андрологиялық тәжірибеде қолдануға жарамды. Липидтер алмасуының бұзылуы көбінесе өмір салты мен этникалық тамақтану әдеттеріне байланысты.

***Түйінді сөздер**: қазақ популяциясының еркектері, жасқа байланысты гипогонадизм, семіздік, тестостерон.*

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Relevance

Number of overweight and obese people is growing at an alarming rate in developed[16] and developing countries around the world[8,10], and the disease is treated as one of the pressing clinical and social health issues of global scale. This is a complex disease considered to be caused by genetic and environmental factors [22]. Currently, 33.0% or 1.3 billion people of the adult population is overweight. If this trend continues, then by 2030 up to 57.8% of the world's adult population or 3.3 billion people is expected to be overweight or obese [21]. At the same time, an important feature of obesity in men is a change in the metabolism of sex hormones [14]. In men, the deposition of adipose tissue occurs mainly in the abdominal part. This is the most important risk factor for the development of hormonal and metabolic disorders, which leads to the development of hypogonadism. [15, 20].

Sex hormones can be one of the factors that determine the distribution of body fat. Current research shows a direct link between hypogonadism and overweight. Obesity is the main reason for the aggravating physiological course of age-related decline in the level of total testosterone and its bioavailable fraction [13]. In the development of obesity, genetic and population factors play an important role (mentality of the population, geographic location, diet and dietary habits) [28, 29].

The real prevalence of obesity among middle-aged and older men is higher. But this category of people is outside the field of urologists. This is due to the low prevalence of older men. A possible reason for the progressive development of complications of the disease in men is the lack of aesthetic claims to the problem of excess weight. Age-related hypogonadism against the background of overweight is a clinical and biochemical syndrome leading to a significant decrease in the quality of life and that negatively affects the function of many systems and organs of an aging organism [5].

The aim is an assessment of the effect of excess weight on the level of testosterone fraction and lipid metabolism in older men of the Kazakh population.

Materials and Methods

Subjects

In total, the study included 300 men who underwent a comprehensive clinical examination to determine the presence of hypogonadism.

Inclusion criteria:

- male;
- age from 35 to 65 years old;
- availability of informed consent to participate in the study.

Exclusion criteria:

- the presence of severe somatic, oncological, and chronic infectious diseases that have a pronounced negative effect on the state of a body;
- a history of acute disorders of the coronary, cerebral, and renal circulation;
- the presence of mental illness, acute conditions;
- the presence of acute infectious diseases in genital and non-sexual spheres at the time of the initial examination;
- BMI indicators below normal weight (<18.5);
- refusal to participate in the study at any stage before the completion of the statistical analysis of the results.

The surveyed were stratified by BMI, divided into 3 groups: with a normal BMI up to 25 kg / m2 (group 1, n = 145), with an overweight BMI from 25-29.9 kg / m2 (group 2, n = 70) and with obesity BMI from 30 kg / m2 and more (group 3, n = 85). BMI was calculated by dividing body weight in kilograms by height in square meters. Weighing was carried out in underwear and socks. The waist circumference was measured directly on the skin at the level of the navel in a standing position. The body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters.

Erectile dysfunction was classified based on the International Index of Erectile Function (IIEF-5), where there is no erectile dysfunction (26-30), mild (22-25), mild to moderate (17-21), moderate (11-16) , severe (6-10).

Ethics approval and consent to participate

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 HDL, LDL, triglycerides, and 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 mIU/ml and 5.41-19.54 nM/L correspondingly.

Bioactive and 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.

Statistical processing of the obtained data was carried out using the Statistica software package (StatSoft Inc. USA, version 7.0). Comparison of groups was performed by nonparametric methods using the Mann-Whitney U-test. The analysis of two quantitative features' relationship was done by the nonparametric method of rank correlation according to Spearman.

Table 1.

Group characteristics.

Parameters	1st group	2nd group группа	3rd group	p
	Up to 25 кгg/м2	Up to25- 29,9 кг/м2	30 кг/м2 and higher	
Age	52,04±7,3	50,4±8,1	47,5±8,2	0,04
BMI	2,4±1,7	27,6±1,1	34,8±3,6	0,01
Waist	88,1±4,3	91,8±4,4	106,2±8,5	0,06
Weight	73,1±7,6	81,1±6,7	101,2±10,2	0,2
Hips	49,0±3,1	50,0±2,4	55,1±3,4	0,5
IIEF-5	26,4±2,5	22,7±4,3	14,2±4,6	0,2

The average age of the subjects comprised 49.9 + 1.43. It should be noted that the groups of men differed in age. If there was no significant difference between the first and second groups (2.04), then the average age of the group of obese men was significantly younger than the previous groups.The increase in BMI at a young age is explained by the influence of hypogonadism. When analyzing the data, it is noticeable that the higher the degree of obesity (BMI), the lower the concentration of total testosterone in the serum of patients. The higher the BMI was, the more pronounced the problems with erectile dysfunction were, although without statistical significance. There were no statistically significant discrepancies between the groups (p = 0.86).

Table 2.

Androgenic status indicators.

parameters	1st group	2nd group	3rd group	p
	Up to 25 кг/м^2	Up to 25- 29,9 кг/м^2	30 kg/м^2 and over	
Total testosterone	12,05±3,4	11,8±3,4	9,02±2,5	0,06
SHBG	36,4±13,8	32,2±13,4	25,8±11,08	0,03
Albumin	42,4±3,8	42,2±5,8	44,5±4,8	0,009
LH	4,3±1,8	3,9±1,9	4,1±2,0	0,6
Free testosterone	1,92±0,5	2,01±0,6	2,24±0,5	0,1
Reference	0,231±0,04	0,221±0,08	0,202±0,05	0,004

Total testosterone in blood serum decreased in men in direct relation to body weight and BMI, although without statistical significance (p-0.06). The level of SHBG negatively correlates with BMI level (p-0.03); the higher the BMI was, the lower the level of SHBG was, so it undoubtedly affected the level of total testosterone. The albumin level in the analysis in all groups did not differ significantly. Luteinizing hormone was within the reference value and had no significant difference between the groups. The value of free testosterone (in percentage and the value of the reference) was worth considering as it was naturally lower in group 2, but in group 3, where the BMI level was highest and the SHBG and total testosterone levels were low, it turned out to be high, although without statistical significance (0.1).

Table 3.

Lipid metabolism indicators.

parameters	1st group	2nd group	3rd group	p
	up to 25 kg/м^2	25 - 29,9 kg/м^2	30 kg/м^2 and over	
Triglycerides	1,8±1,8	1, 9±1,9	2,7±1,5	0,3
LDL	3,2±0,7	3,37±0,6	3,8±0,7	0,08
HDL	1,6±1,6	1,19±0,39	1,3±1,3	0,001

The concentration of triglycerides and LDL in the serum of the subjects was higher than normal in direct proportion to the BMI. A negative correlation was observed in HDL and BMI indicators with statistical significance (0.001).

Discussion

It is known that most men accumulate visceral fat with age due to the maintenance of the usual diet and a decrease in physical activity. Results showing the negative effects of fat and obesity on total testosterone and SHBG can be found in many publications [11, 23].

In our study the total testosterone level decreased proportionally in direct relation to BMI. So, with overweight, it was lower than with normal one, and with obesity, the concentration of the hormone was significantly less relative to men, not only with normal, but also with overweight. We determined that the reason for the accumulation of visceral fat is not the calendar age itself, but the influence of androgenic status.

Total testosterone levels are directly related to SHBG concentration. Due to the very high ligand binding affinity, plasma SHBG is the main protein for testosterone transport. Changes in blood SHBG levels affect the distribution of testosterone in plasma and its availability to tissues and target cells [17].

Traditionally, SHBG is not considered as a risk factor for the development of any disease (e.g.: prostate cancer, type 2 diabetes, cardiovascular disease), as it is treated as a sequestration of hormones to control their bioavailability. In recent publications there are two opposite statements concerning the level of SHBG in hypogonadism [19]. So, with increasing calendar age the level of SHBG also expands, that causes a decrease in the free fraction T, while maintaining a normal level of total T. In obesity the concentration of SHBG decreases [6].

The results of our research have proved the validity of both statements. There is a significant negative correlation between SHBG and BMI and a positive relationship between SHBG and age. Thus, in group 1 with normal BMI, there was an increase in SHBG levels (36.4 + 13.8) with a decrease in the level of total testosterone to the lower limit of physiological parameters (12.05 + 3.4). And in the group with the maximum BMI, on the contrary there was a decrease in the concentration of SHBG (25.8 + 11.08). In both cases, there is a drop in the concentration of total testosterone (12.05 + 3.4; 11.8 + 3.4; 9.02 + 2.5).

The mechanism by which obesity is associated with a decreased level of SHBG is not fully understood, but it may include suppression of SHBG synthesis in the liver by increased insulin concentrations [2].

Accordingly, a decrease in the level of SHBG may be a predictor of the development of metabolic syndrome and diabetes mellitus [3] in combination with a decrease in total testosterone.

Recent studies have shown the existence of a SHBG gene polymorphism that functionally affects its affinity for androgens and estrogens. In polymorphic variants of SHBG, a decrease in other biochemical properties is also possible. A drop in the circulating SHBG carrier protein leads to a decline in the concentration of total testosterone [25].

An age-related increase in SHBG secretion leads to a slight decrease in the content of total testosterone in the blood serum, while as a result of a decline in testosterone secretion in the testes, the content of biologically active and free testosterone decreases, which accelerates androgen deficiency in body. The fraction of circulating testosterone that is not bound to any plasma protein is called the free testosterone fraction. The term *bioavailable testosterone* refers to the fraction of circulating testosterone that is not associated with SHBG, and is largely the sum of free testosterone and testosterone associated with albumin.

Testosterone has a weak affinity with albumin, which allows it to be easily cleaved (dissociated) in tissue capillaries and be effectively available for biological activity [4].

We calculated the levels of free and bioavailable testosterone based on measurements of total testosterone, SHBG and albumin using the formula for calculating free testosterone according to A. Vermeulen.

In our study the percentage of free testosterone correlated negatively with total testosterone, SHBG, and BMI. But the study has found that calculated free testosterone was higher in the high BMI groups. But the reference value of free testosterone according to the literature data was directly proportional to the level of total testosterone and BMI.

In all groups the reference value of free testosterone is directly correlated with erectile dysfunction, possibly due to a high degree of testosterone degradation and a small depot of total testosterone. Total testosterone in obesity decreases along with the concentration of SHBG, providing compensation for the bioavailable fraction [1, 26].

Adipose tissue has a complex organization, in which adipocytes interact with blood vessels and nerves that determines their high hormonal and metabolic activity. The cycle of converting testosterone to estradiol is taking place in fat cell.

The age-related decrease in total testosterone according to the feedback mechanism leads to an increase in luteinizing hormone. The LH level provides information about the functional status of the gonads. Our data show that this theory functions in men with normal weight. In excess weight, there is a decrease in luteinizing hormone and the aromatase activity of excess adipose tissue converts testosterone to estradiol. Estradiol has an inhibitory effect on LH and inhibits the secretion of

gonadotropic releasing hormone [7]. Ultimately, this is manifested by a decrease in the level of testosterone in the blood, in other words, by secondary hypogonadism [24].

Total testosterone and SHBG are significantly associated with abdominal obesity and high triglyceride concentrations [5]. It is known that an increase in insulin concentration expands the content of triglycerides and low-density lipoprotein cholesterol (LDL cholesterol) and reduces the level of high density lipoprotein HDL cholesterol [12].

Our study has discovered a direct correlation between BMI and triglyceride and LDL levels, and an inverse relationship with HDL levels [27].

Low HDL concentrations are metabolically associated with high triglyceride and HDL concentrations.

HDL is considered to be an antiatherogenic factor. Low concentrations of HDL cholesterol may be associated not only with the early development of atherosclerosis, but also with a worsening prognosis for people with heart disease.

The negative effects of low HDL content depend on a variety of medico-social causes and are closely related to the overall risk of cardiovascular disease in urbanized societies where people are mostly keep sedentary lifestyles and consume large amounts of animal products.

Taking into account the mentality of the Kazakh population, increased consumption of animal fats and lipid profile changes are not surprising. There is a natural relationship with BMI noticed, when with increasing body weight the triglyceride and LDL levels also accelerate [18]. As for HDL, depending on weight its indicators are lower. The number of people living in cities, where there is an excess calorie content of food opposed to level of body energy consumption, is increasing year by year. Energy costs depend on the degree of activity (primarily physical) and person's lifestyle. Lack of physical activity is one of the important causes of obesity.

We believe that lipid metabolism disorders are a consequence of ethnic eating habits. Food is mainly represented by fatty meat food and limited consumption of plant foods. Currently, the nutrition of indigenous people is characterized by the presence of a large amount of canned and synthetic products [9], the consumption of foods with a high content of saturated and trans fats, which can lead to changes in lipid metabolism and contribute to the development of pathology, including obesity [30].

To summarize the results of our study, we can say that the value of SHBG is underestimated by urologists when treating older men with hypogonadism on the background of overweight. SHBG values can have diametrically opposite values. In older men at normal weight there is an increase in the concentration of SHBG, while in men with obesity a decrease in its concentration is noted. When interpreting the results, one cannot exclude the factor of SHBG protein polymorphism, which can be functionally inconsistent even at normal concentration. Not only a decrease in the level of SHBG as a depot of testosterone, but also a reduction in testosterone secretion and a deficiency of the bioavailable fraction are the causes of hypogonadism in older men.

Most formulas for calculating the bioavailable fraction of testosterone represent low level of accuracy, which must be taken into consideration by clinicians when diagnosing age-related hypogonadism. Reliable tests due to their complexity and cost are not always available to practicing clinicians.

Therefore, to make informed clinical decisions, algorithms based on available laboratory methods and clinical manifestations of hypogonadism are needed, considering the fact that testosterone deficiency itself in older men can occur under the guise of many somatic diseases. These steps will reduce the risk of misclassification of the disease and optimize clinical decision in treatment of androgenic disorders in older men with overweight and obesity.

Conclusion

Overweight and obesity are accompanied by a decrease in SHBG and total testosterone levels and their decline correlates to the degree of obesity.

SHBG is the main driver of this relationship, taking into account its sensitivity to insulin levels. Despite of the fact that calculated figures of free testosterone do not have a solid biological basis, they are entirely suitable to be used in andrological practice. Clinicians need to consider errors when interpreting free and bioavailable testosterone levels. Lipid metabolism disorders are more often caused by lifestyle and ethnic eating habits.

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