XVII INTERNATIONAL ISSAM CONGRESS
Hypogonadism as a trigger factor for inflamaging.
From chronic hypoxia pandemic to oncology pandemic
30 nov. - 01 dec. 2023. Kyrov, Russia

SPEAKER / Aleksandr Dzidzaria

"Low or high SHBG - which is more dangerous ?"

Who is he?

-Biological effects of sex steroid hormones depend significantly not so much on their total blood fraction as on the plasma concentration of free (bioavailable) steroids

-SHBG levels (a trap protein that irreversibly binds testosterone).
-albumin

- Drug-mediated factors
- Hormonal and metabolic factors
- Genetic determinant
- Non-hormonal factors

take into account when studying Metabolism and assessment of clinical effects of sex steroid hormones in both sexes

SHBGs: structure, sites of synthesis in the body, and affinity for sex steroids.

is located on the short arm of chromosome 17 is

polypeptide with a molecular mass of 43-44 kDa

expressed in most vertebrates

373 amino acids

A separate fraction of SHBG, androgen-binding protein (ABP) (produced in Sertoli and Leydig cells and cardiomyocytes), regulates the local bioavailability of androgens

Androgens and estrogens competitively interact with the same steroid binding site in hsCRP

SHBGs: structure, sites of synthesis in the body, and affinity for sex steroids.

A zinc atom located at the entrance to the steroid binding site of human SHBG specifically reduces its affinity for estrogens

Free zinc concentrations in plasma are very low, but it can be taken up in extravascular tissue compartments such as the prostate gland and male reproductive tract, where zinc levels are exceptionally high

the main (classical) site of SHBG synthesis is traditionally considered to be the liver

Metabolic diseases with liver involvement in the pathological process (obesity, insulin resistance, metabolic syndrome, hepatitis, liver cirrhosis, etc.) lead to a significant change in SHBG levels

SHBGs: structure, sites of synthesis in the body, and affinity for sex steroids.

SHBG synthesis has also been detected in adipose tissue, prostate gland and brain (hypothalamus and pituitary), where it is spatially closely related to **oxytocin-producing** neurons

Extrahepatic SHBG has a local control function
bioavailability of sex steroid hormones

Affinity of different sex steroids for SHBG

affinity for dihydrotestosterone (DHT)>affinity for testosterone>affinity for androstenediol>affinity for estradiol>affinity for estrone

DHT has the highest affinity for SHBG, which is about 5-fold higher than for testosterone and about 20-fold higher than for estradiol

dehydroepiandrosterone (DHEA) binds weakly to SHBG

Serum dehydrotestosterone sulfate (DHEAS) is virtually unbound to it

androstenedione binds exclusively to serum albumin

Factors affecting SHBG levels

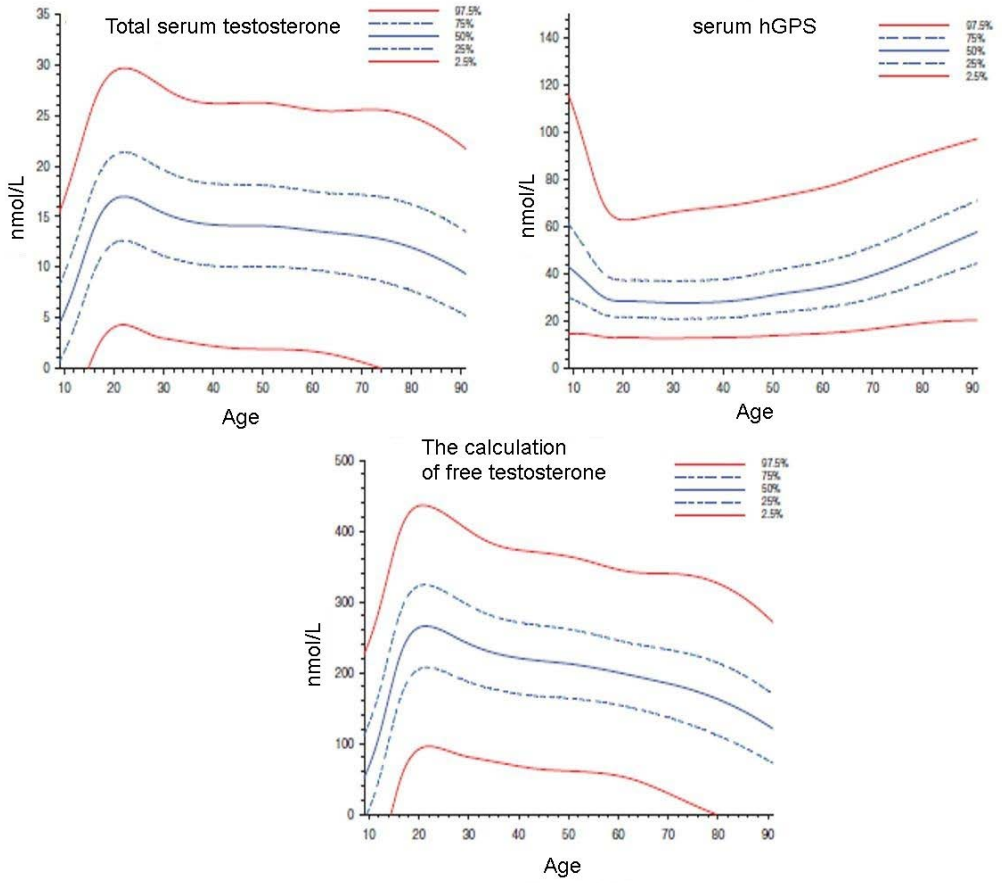
Norms: in the literature in the range of values 13-71 nmol/l, and women - on average 1.5 times higher (18-114 nmol/l), with the assumption that the serum concentration of SHBG in the norm approximately corresponds to the age of a healthy man, and the increase of SHBG above the specified reference in men is one of the laboratory signs of age-related male hypogonadism

Kalinchenko S.Y., Tyuzikov I.A., Tishova Y.A., Vorslov L.O. Examination of a man. Moscow: Practical Medicine, 2014. 112 c

Identified factors affecting the level of SHBG

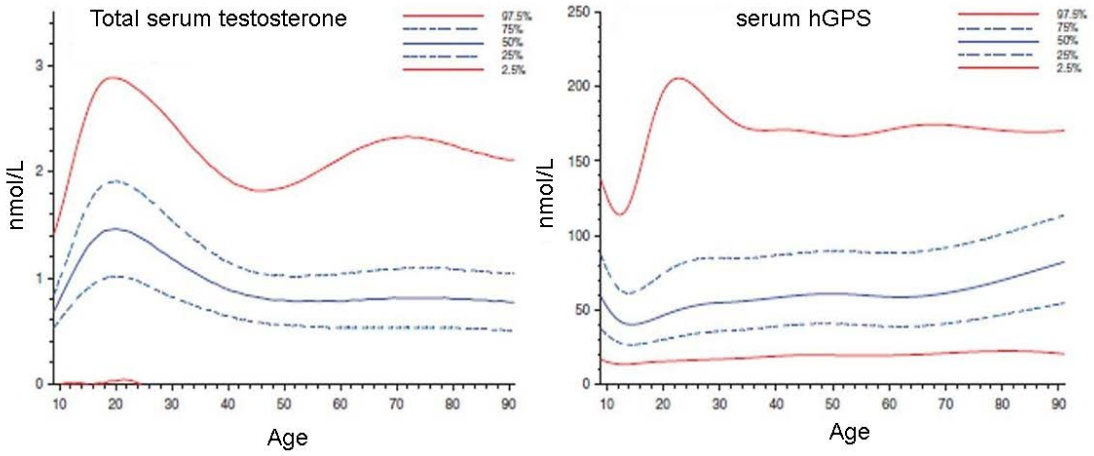
Increase hspsg levels	Reduce hspsg levels
Adiponectin	Acromegaly and growth hormone excess
Age Hepatitis	Androgens and androgen therapy Anti-
Hyperthyroidi	estrogens
sm	Gestagens
Growth hormone deficiency	Hyperinsulinemia/insulin resistance
Testosterone deficiency	Hypothyroidism
Estrogen excess Anorexia	Corticosteroids
nervosa	Monosaccharides (glucose and fructose)
Synthetic PPARγ ligands	Malnutrition (protein deficiency) Nephrotic
(thiazolidinediones)	syndrome
Phentoin	Obesity and overweight Pro-inflammatory
Physical activity Liver	cytokines (TNF-α and IL-1β)
cirrhosis	Prolactin

Age-related dynamics of SHBG levels in men and women.



pronounced pubertal increase in the level ofserum testosterone in men, which reaches a maximum at the age of20 and further stabilizes by the age of 40 years, after which its level becomes fluctuating, significantly decreasing at the age of over 70 years -Handelsman D.J. et al.

SHBG levels decline to a minimum in men in their 20s

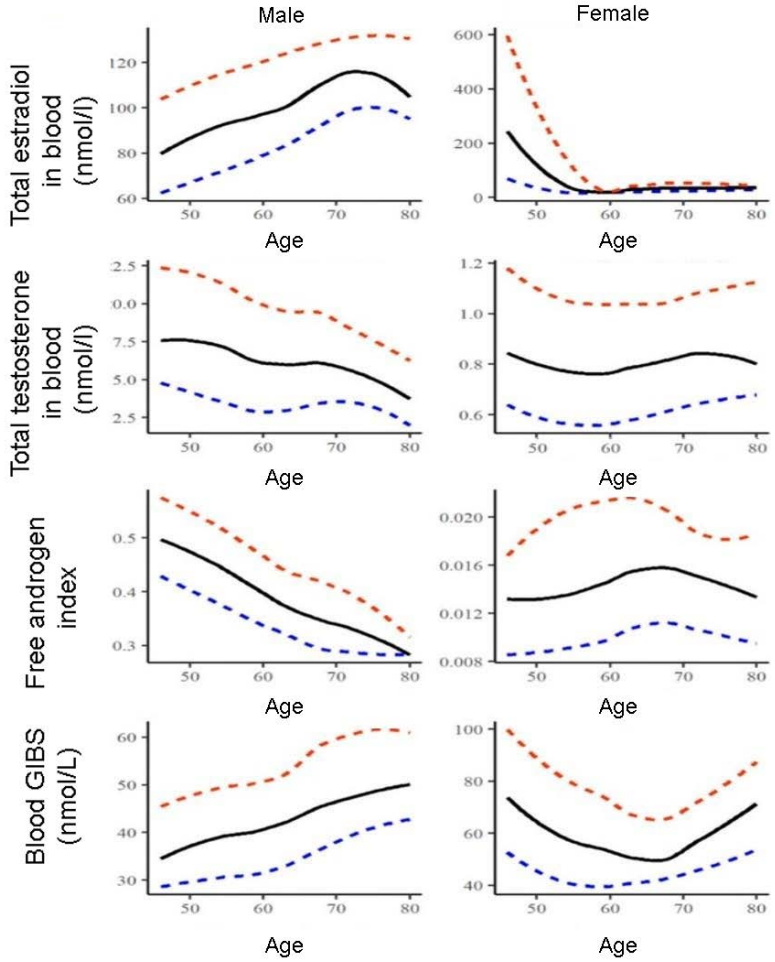


According to the researchers, among men, total estradiol and SHBG showed an increasing trend starting at age 45. In women, total estradiol and SHBG showed a decreasing trend from age 45 to 60, and SHBG showed an increasing trend starting at age 60.

Age-related dynamics of total/free testosterone and SHBG in men and women

obvious sex differences in the dynamics of SHBG levels with age. While SHBG levels increase in men from 45 years of age, a U-shaped dependence is observed among women.

The decrease in SHBG levels in women after age 45 reflects a parallel decrease in estradiol levels; the observed increase in SHBG levels from age 60 onward is still unexplained and deserves further study



Scientific evolution of ideas about the biological functions of SHBGs

The classical hypothesis (theory) of free hormones (Mendel C.M. in 1989 Ms. the biological activity of a particular hormone is influenced by its unbound (**free)** fraction, but not by the fraction bound to plasma proteins.

The free hormone hypothesis is probably not true for all hormones in relation to all tissues

true for all tissues with respect to thyroid hormones, cortisol and hydroxylated vitamin D metabolites

""free hormone hypothesis""

Circulating SHBG is not only a passive carrier (transporter) of sex steroid hormones but also actively regulates testosterone uptake and androgen signaling in some tissues -*Khan M.S., Hryb D.J., Hashim G.A., et al.* Delineation and synthesis of the membrane receptor-binding domain of sex hormone-binding globulin. J Biological Chem.

SHBG can also directly release hormones in certain tissues and cells, which can affect both the production and action of sex hormones, as well as the expression and function of circulating SHBG

Intracellular expression of SHBG in testicular proximal seminal tubule cells increases dihydrotestosterone uptake and prolongs androgen-sensitive gene expression-Hong *E.-J., Sahu B., Jänne O. A., Hammond G.L.*. Cytoplasmic accumulation of incompletely glycosylated SHBG enhances androgen action in proximal tubule epithelial cells. Mol Endocrinol. 2011

Stepping out of your comfort zone

SHBG may even "exit" from the systemic circulation into some tissues and interact directly with proteins on the plasma membranes of certain cell types, and that this may contribute either to the delivery of SHBG-related sex steroids via endocytosis mechanisms or to the transmission of signals mediated by cell membrane receptors involving the activation of membrane regulatory proteins such as megalin/cubilin - *Avvakumov G.V., Cherkasov A., Muller Y. A., Hammond G. L*. Structural analyses of sex hormone-binding globulin reveal novel ligands and function. Mol Cell Endocrinol.

SHBG gene polymorphism

The polymorphisms described	Frequency according to databases	Amino acid-lot changes	Effect on the synthesis and/or activity of HSPCs
rs373254168	0.00008	T7N	Loss of O-glycosylation
rs143521188	<0.00008	T48I	Inefficient dimerization / impaired Ca^{2+} binding / decreased affinity for DHT
rs6259	0.09	D327N	Produced / Additional site N-. glycosylation / normal steroid binding
rs373769356	0.00008	R123C	Decreased affinity for DHT / Increased estradiol affinity
rs143269613	0.00008	R123H	Decreased affinity to DHT / increased affinity to estradiol
rs368589266	0.00008	R135C	Increased affinity for estradiol
rs6258	0.006	P156L	Reduced affinity for testosterone
rs145273466	0.0005	L165M	Increased affinity for estradiol
rs372114420	0.00008	E176K	Increased affinity for estradiol
rs146779355	0.00008	G195E	Low secretion / reduced affinity for DHT
N/A	Unknown	G195R	Lack of secretion

SHBG as a promising biochemical marker of human pathology

Serum hsps levels may in the future be a new potential biochemical marker of various age-associated diseases and biological aging in general - *Goldstajn M.S., Toljan K., Grgic F., et al. al.* Sex hormone binding globulin (SHBG) as a marker of clinical disorders. Coll Antropol.

3264 men and women from a large population-based cohort study

Aribas E. et al. (2021)

distribution of serum SHBGlevels by age, we calculated the total score of cardiovascular risk factors and investigated the average levels of SHBG

Participants with more cardiovascular risk factors had lower levels of SHBG, and when stratified by age, older participants had higher SHBG levels

2913 men

Analysis of morning blood samples for testosterone (T), dihydrotestosterone (DHT), estradiol (E2) (mass spectrometry) and SHBG (immunoassay)

That the average difference over the decade was -0.46 nmol/L for T, -0.11 nmol/L for DHT, -7.5 pmol/L for E2, +10.2 nmol/L for SHBG, and -0.065 for leukocyte telomere length

SHBG had an inverse correlation with telomere length (r = -0.053, P = 0.004In elderly men, neither T nor DHT levels were associated with leukocyte telomere length.

AGING PROTEIN!!!

Yeap B.B. et al (2019).

AN AGING MARKER?

167,706 British men

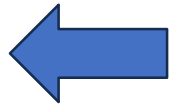
serum total testosterone and serum SHBG levels were inversely associated with standardized leukocyte telomere length in a multivariate analysis, meaning that men with higher levels of total testosterone or SHBG had shorter telomeres, which, according to the researchers, refutes the protective role of testosterone in slowing biological aging in men

Marriott R.J., Murray K., Budgeon C.A., et al. Serum testosterone and sex hormone-binding globulin are inversely associated with leucocyte telomere length in men: a cross-sectional analysis of the UK Biobank study Eur J. Biol. Endocrinol. 2023.

The culprit of cancer and other diseases?

According to Liang G. et al. (2021), it was the level of SHBG that had the strongest correlation with clinical manifestations of age-related male hypogonadism, so it is its level that can be used in the near future as an early predictor of the onset of symptomatic age-related hypogonadism in men

Male infertility, erectile dysfunction, male hypogonadism, prostate cancer and a number of other diseases of the male sexual and reproductive system



SHBG

Sialignal protein

Biswas S., Mita M.A., Afrose S., et al. Integrated Computational Approaches for Inhibiting Sex Hormone-Binding Globulin in Male Infertility by Screening Potent Phytochemicals. Life (Basel). 2023

Three new drugs, cryptomysrin, dorsilurin E and isoiguestrin, were identified as potential SHBG inhibitors with binding affinities of -9.2, -9.0 and -8.8 kcal/mol, respectively.

They have higher binding affinity than the control drug anastrozole (-7.0 kcal/mol).

In addition to favorable pharmacological properties, these top three phytochemicals showed no side effects in pharmacokinetic evaluations

SHBG is not a marker, it's a cause.

Slide Text

HSPG functions as a true hepatokine, at least in women, by reducing the risk of developing mellitus type 2 diabetes

Pharmacologic therapies that increase serum SHBG levels, such as, for example, de novo lipogenesis inhibitors or thyroid hormone receptor β-agonists, may provide promising avenues for the treatment and prevention of type 2 diabetes mellitus in both sexes and polycystic ovary syndrome in women

Simons P.I.H.G., Valkenburg O., Stehouwer C.D.A., Brouwers M.C.G.J.. Sex hormone-binding globulin: biomarker and hepatokine? Trends Endocrinol Metab. 2021.

Prostate cancer and SHBG

Genetically determined higher levels of SHBG were causally associated with a lower risk of prostate cancer and inversely associated with bioavailable testosterone levels. Moreover, a one standard deviation (59.5 pmol/L) increase in bioavailable testosterone levels was significantly associated with a 22.0% increase in overall prostate cancer risk

Wan B., Lu L., Lv C. Mendelian randomization analyses identified bioavailable testosterone mediates the effect of sex hormone-binding globulin on prostate cancer. Androl. 2022

Conclusions

1. Our classical view of it solely as a sex steroid hormone transporter protein is changing dramatically
2. New genetic studies have revealed specific features of the structure of the SHBG molecule, demonstrating the key role of calcium and zinc chelates in regulating its activity
3. SHBG gene polymorphisms, may have an impact on the assessment results and diagnostic value of serum SHBG determination in routine practice.
4. Abnormalities in serum SHBG levels have been associated with the risks and consequences of various diseases associated with abnormal exposure to sex steroid hormones
5. Serum levels of SHBG can be used as a potential biomarker of disease onset or disease severity
   SHBG is not only significantly correlated with some age-associated diseases, but SHBG itself may play a direct role as one of the independent pathogenetic mechanisms of these diseases
6. SHBG is a promising universal biochemical marker of human aging