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Review

Sex hormone binding globulin (SHBG) as a marker of clinical disorders

Karlo Toljan[1], Franjo Grgić[2], Dinka Pavičić Baldani[2], Ivana Jurković[2], Marina Šprem Goldštajn[2]

[1] University of Zagreb, School of Medicine, Zagreb
[2] University of Zagreb, School of Medicine, Department for Gynecology and Obstetrics, Zagreb

ABSTRACT

Sex hormone binding globulin (SHBG) is an important protein, not only for transporting sex steroids which is its primary role, but with the discovery of a specific receptor that binds SHBG, a novel approach regarding classic 'free-hormone hypothesis' should be implemented. Research in SHBG gene and it expression has been done, as well as cellular signaling that controls it. It provides significant knowledge of the impact of certain well –defined cellular level signaling pathways and how they affect the level of SHBG production. Moreover, new insights have proven that SHBG isn't just a peripherally synthesized protein. Its origin has been proven to exist in the brain, namely in the hypothalamus and the pituitary, where it is spatially closely related to oxytocin-producing neurons. The main peripheral organ that produces SHBG is the liver. Since the liver is the central metabolic organ, certain metabolic diseases will result in changed SHBG serum levels. On the other hand, endocrine disorders that affect tissues involved in sex hormone regulation will also have an impact on SHBG levels. Thusly, SHBG stands as one of the mediators between various endocrine tissues and definitely contributes with its own pathophysiological role in diseases such as: obesity, metabolic syndrome, polycystic ovary syndrome, osteoporosis, breast and prostate cancer. Its value expands to the area of clinical medicine as a marker of certain pathological states. Some studies already established its reliability and the growing trend to implement it as a useful clinical marker is present. It still remains largely understudied, from physiological and clinical aspect, but recent findings give notions that SHBG plays an important role in health and disease and could be a useful assessment marker.

Key words: *Sex Hormone-Binding Globulin, Nutritional Status, Polycystic Ovary Syndrome, Fatty Liver, Biomarkers*

Introduction

Sex hormone binding globulin (SHBG) is a glycoprotein transporting steroid hormones which has the highest affinity for androgens, namely dihydrotestosterone (DHT) and testosterone, and up to five times lesser affinity for estrogens, thus representing the key transport vehicle for these sex steroids[1]. In addition to non-specific carriers such as albumin, SHBG concentration primarily regulates the availability of the aforementioned steroids. The postulate known as 'free-hormone hypothesis' states that the 'bioavailable' hormone, i.e. the one having an effect when it binds to its receptor, is the unbound or 'free' fraction of the hormone[1]. However, new experimental evidence have proven that SHBG itself can elicit a response by binding to its respective receptor[2,3], as well as change the usual response to the steroid hormone on the target cell, depending on whether it was bound before or binds after SHBG already reached its own receptor (SHBG-R)[2-5]. These findings demonstrate that SHBG isn't just a passive plasma carrier, but a molecule with significant activity in different bodily tissues[2-5]. This article will focus on presenting the proven role of SHBG in certain pathophysiological states, especially the ones that could be influenced by the direct effects of SHBG when bound on SHBG-R. Consequently a use of SHBG as a marker in pathological states stems from its changing concentration due to an ascertained cause.

SHBG gene and regulation of expression

The *SHBG* gene is located on the short arm of chromosome 17 (17p13.1)[6] with constant exons 2-8 and a variable exon 1, which can be present in six possible variations, altogether adding up to a sum of 13 exons[7]. A single SHBG subunit consists of 373 amino acids[7,8], but is present as a homodimer in its full form, having two available binding sites for hormones[9]. Regarding its glycosylation, it con-

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tains one O-linked and two N-linked oligosaccharide chains[10,11] as well as a possible third N-glycosylation site that arises from a mutation in exon 8 and provides an additional property of having a reduced clearance rate[12]. The human tissues in which transcription of the *SHBG* gene occurs are: testis, liver, breast, brain, endometrium, ovaries, prostate[3,7,13]. Besides these sources, for research purposes, cancer cell lines from prostate, breast and liver tissue are used, as well as transgenic mice expressing a human *SHBG* transgene[7,14]. Single nucleotide polymorphisms in the *SHBG* gene which have a measurable effect on plasma SHBG concentration exist. The reference sequence (rs) 6257 being CC or CT instead of wild-type TT, resulted in a 10% decrease in the SHBG level, while rs 6259 being AA or AG resulted in a 10% increase in plasma SHBG[15]. A protein named hepatic nuclear factor 4 alpha (HNF-4α), is a key factor that increases *SHBG* expression[16,17], while the chicken ovalbumin upstream promoter-transcription factor (COUP-TF) decreases it[17] as well as peroxisome proliferator-activated receptor gamma (PPARγ)[18]. On the molecular level, factors that increase *HNF-4α* gene expression are thyroid hormones[19], estrogens[16], AMPK and ß-oxydation induced by adiponectin receptor activation[20,21]. On the other hand, molecular cascades that decrease *HNF-4α* gene expression are mediated by NFκB[22] and c-Jun, raised by activation of TNFα[22,23] receptor and IL-1ß receptor[24] respectively. High carbohydrate diet that promotes lipogenesis and lowers ß-oxidation also inhibits *HNF-4α* gene expression[4,25]. PPARγ production is inhibited by oleate[4,26] via lowering its genetic expression and this has been reported on a 'macroscopic level' in clinical data through correlation of olive oil intake and increased SHBG levels[26].

Central and Peripheral Roles and Effects of SHBG

When discussing SHBG, most of the research is done in context of a assessing its concentration in blood or peripheral tissues, while the aspect from central regulation, i.e brain is an entirely different topic rarely mentioned. It would be valuable to consider the role of neurosteroids[27] in terms of the brain as the generator of behavior and thusly being involved in various pathological states that are linked with changed levels of SHBG and peripheral hormonal dysfunction, but also not omitting a vice versa effect[4,5,13]. SHBG has been confirmed to exist in human hypothalamus, median eminence and infundibulum, namely in the perikarya of neurons, nerve fibers and ependymal cells, but not in the nuclei[13]. Since SHBG regional expression was co-localized with neurons expressing oxytocin, it has been proposed that brain produced SHBG is also sent through axonal transport to the posterior pituitary[13]. Through measuring molecular weights, a 53-kDa and a 49-kDa SHBG protein was noted, the heavier found in serum and the other in cerebrospinal fluid (CSF). The lighter SHBG protein was also found to be the one produced in the hypothalamus leading to the proposition that the CSF levels of SHBG protein are of brain origin[13]. Substantial evidence confirm that peripherally produced sex hormones end up in the brain, but are differently taken up by neurons depending on the sex hormone type and receptors expressed[13,28,29]. The decreases in hormone production has been linked with symptoms of brain aging and declining cognitive performance including Alzhemier disease[5,30]. Glial cells in the brain also represent major targets for sex hormones which results in indirect effect on neurons[31]. This demonstrates the importance of sex hormones for brain health and since SHBG is directly involved in sex hormone transport, changes in one's hormonal and SHBG status tones the behavior and mood on account of those being the results of neuronal output.

Peripheral organ that is the main producer of SHBG is the liver[1-3]. Androgens and estrogen may be carried either by SHBG or albumin, or remain unbound as the traditionally known 'free' fraction[1]. In regards to liver's prominent role in whole body metabolism, any primary or secondary hepatic pathological state that affects it significantly will express as a deviation of SHBG levels and consequentially sex hormone imbalance. It should be also kept in mind that sex differences make a considerable difference when dealing in topics regarding SHBG. Even though the prepubertal SHBG concentrations are similar in both sexes[32], in adult population, the female levels are as twice as high as the male[32]. In senescence however, male SHBG levels tend to increase by 1.1% yearly[32,33] and female tend to drop[32]. The cellular mechanisms which can represent a few 'final common molecular pathways' have already been discussed and due to different etiologies and pathogeneses for certain organ systems on a grander scale, all associated with variable SHBG levels, a separate explanation is warranted.

Uses of SHBG in Various Pathophysiological States

Nutritional status

SHBG serum levels are higher in individuals suffering from anorexia nervosa[34-37]. It was found that in those individuals, SHBG levels were inversely correlated with weight gain and no correlation was observed in relation to the hormonal status, namely levels of gonadotropins, estrogen, testosterone, triiodothyronine[36,37]. Restoring body mass in anorexic individuals was followed by a decrease in SHBG serum levels[34,36,37]. Interestingly, high SHBG levels have been confirmed in pathological states of anorexia nervosa and kwashiorkor, while not in marasmus[35]. After measuring inflammation with C-reactive protein as a marker, and glomerular filtration through cystatin-C, the same conclusion was still reached for marantic patients, since these two markers used haven't shown correlation with SHBG levels[35]. As follows, SHBG represents a reliable value in assessment of refeeding in diseases such as anorexia nervosa[34-37] and kwashiorkor, but not in marantic state[35]. In the latter case SHBG can be used to differentiate it from the aforementioned diseases[35].

Obesity is linked with lover serum levels of SHBG in both men[38] and women[39]. Even after adjustment for an

age-linked increase in men, the levels of SHBG still declined when obesity was present. In child population, obesity and chronic inflammation lowered SHBG levels[40], which anticipated earlier puberty onset – a more common feature in present time[41-43]. Estrogen and androgen levels change accordingly to the 'free hormone hypothesis', which means a larger fraction of unbound hormone is 'bio-available' to exert its effect that is clinically noticeable. With the arising future clarification for the role of SHBG as an active protein in cellular signalization more details about the physiology of puberty onset are destined to come.

Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of features that shows a general dysfunction of the physiology of cellular metabolism. It is linked with central obesity and insulin resistance as the etiological factors[44,45]. The criteria for a clinical diagnosis also include hypertension and dyslipidemia[46]. The affection of the liver as the main metabolism-regulating organ has profound pathophysiological consequences. Liver steatosis or non-alcoholic fatty liver disease (NAFLD) is a common feature in metabolic syndrome and the leading etiology for liver dysfunction[47]. The state of metabolic syndrome is a vicious circle where hyperglycemia and dyslipidemia are aggravated with increasing insulin resistance and liver fat accumulation. This ultimately leads to chronic inflammation[46, 48-50] with lower levels of anti-inflammatory cytokines (e.g. adiponectin) and higher levels of proinflammatory cytokines (IL-1, IL-6)[4]. Consequently, unfavorable signaling cascades are triggered in hepatocytes. Regarding the role of the liver in the production of SHBG, the levels of this protein drop significantly in individuals with MetS[39,51,52] and SHBG levels can even serve as a predictive value for pubertal children developing metabolic syndrome and obesity in adulthood[53]. The role of SHBG for being a sensitive biomarker for MetS comes from the evidence that monosaccharide induced lipogenesis, especially with higher fructose intake, regulates the expression of *SHBG* gene in the liver[16,54] and decreases the hepatic production of SHBG. Weight loss is followed by an increase in SHBG serum levels. In postmenopausal women with visceral obesity, a greater decrease in leptin concentrations was linked with lower initial SHBG concentration preceding a weight loss, independent of total amount of weight lost[55]. Weight reduction in peripubertal obese children was followed by an increase in SHBG concentrations and more favorable arising pubertal traits[56] (virilization in males and less virilizing in females). In adult obese male population, SHBG levels increased and were correlated with weight loss as well as the general reproductive health features, i.e. sperm count, semen volume and testosterone levels[57]. In obese patients, SHBG levels serve as an indicator of total adiposity, rather than disrupted insulin regulation[58]. MetS is linked with a combined pathophysiology of Type 2 Diabetes (T2D) and cardiovascular disease (CVD) and is associated with a higher risk for developing both of these in an affected individual[46].

Cardiovascular risk

Cardiovascular risk is different sex-wise, with the male population being at a greater risk, while women enjoy the cardioprotective role of estrogens[59,60] up until reaching postmenopause when these risks are believed to be equalized. Even though, recent evidence support that by maintaining normal testosterone levels in men, a cardioprotective effect is exhibited[61]. Both estrogens and androgens are transported primarily by SHBG, so obviously the changing levels of serum SHBG must have an important role in predicting the cardiovascular risk, according to sex, age and hormonal status of the individual. In the renowned Framingham score, total cholesterol and HDL cholesterol are important contributors to total calculated cardiovascular risk[62]. For SHBG, it has been shown to be positively correlated with HDL levels, and inversely with insulin and triglycerides[63]. Even more intriguing is that the HDL uptake via its receptor seems to be involved in SHBG cellular uptake in in steroidogenic cells[5]. Whether SHBG is needed in steroid synthesis since HDL represents a steroid precursor still remains unresolved. All in all, low SHBG concentrations seem to be associated with a worse cardiovascular state through promoting the imbalance of usually bound hormones and by generally lower activation of HDL receptor stemming from low blood HDL concentration. Since the risk for cardiovascular disease is higher in individuals suffering from MetS[44,46,47], in which SHBG has been shown to be lowered, a joint pathophysiological process combines these diseases. It has been demonstrated in a 12-year long follow up that a decrease in SHBG represents a significant risk factor in overall mortality[64,65]. SHBG stands as an available marker for assessment of cardiovascular health, especially in female population[66]. Future implications might be even broader regarding cardiovascular risk assessment and the importance of SHBG in cardiovascular pathophysiology, since this protein is produced by cardiomycocytes in patients suffering from dilated cardiomyopathy and appears to be internalized by them possibly representing a mechanism for delivering sex hormones to heart muscle[2].

Breast, prostate, ovarian and endometrial cancer

The pathophysiological role of SHBG and its receptor is particularly important in terms of studying how breast cancer cells behave in relation to estrogen and SHBG levels. When SHBG is bound to its receptor on an estrogen-dependent breast cancer cell and when estrogen binding subsequently follows, an increase in cellular cyclic adenosine monophosphate is noted and Protein kinase A is activated[3]. This could indicate that SHBG-R is a G-protein membrane receptor. Further signalizing possibly through MAP kinase pathway isn't elucidated, but by modifying cellular behavior, a clear inhibition of usual proliferative estrogenic effect on breast cancer cells is seen, however only if SHBG binds to its receptor prior to binding with estrogen[67]. Estrogen-positive breast cancer cells bind

SHBG twice as often as estrogen-negative cells, where only an average of 37% of breast cancer cells bind this particular glycoprotein[3,67]. Another mechanism for cancer protection involves the mere binding by SHBG of otherwise 'free' estrogen, which lowers estrogen levels that could potentiate growth in breast cancer cells. The 'free hormone hypothesis' is definitely updated in oncology by provided evidence that not only the hormone levels, but its binding proteins also, have an impact on cancerous growth. A meta-analysis from 2015[68] showed that SHBG levels are significantly associated with a lower breast cancer risk, moreover being a protective factor for developing this disease. In a randomized trial[69], application of low dose tamoxifen has been linked with increased SHBG serum levels and followed by a decreased risk for developing breast cancer. Weight loss which lowers estrogen production by reducing the size of a secondary endocrine organ, the white adipose tissue, and which increases overall SHBG levels has a positive effect in secondary prevention of breast cancer, i.e. recurrence or poorer prognosis[70].

In the prostate, the binding of estrogen to the already receptor bound SHBG induced PSA production, an effect which could be blocked by antiandrogens and not anti-estrogens[3]. It suggests that the same signalization as in breast cancer cells has a different final effect, i.e. it doesn't exert an anti-proliferative effect. In vitro and pathological analyses provide findings that support the correlation between *SHBG* expression in prostate tissue and more advanced cancerous features, be it microscopically or in terms of general disease progression[71]. SHBG after radical prostatectomy, as a predictive factor for biochemical cancer recurrence, improves predictive accuracy[72]. On the contrary, in men without prostate cancer, SHBG levels were inversely correlated with PSA concentration[73]. A biopsy cohort study[74] concluded that SHBG shouldn't be regarded as a predictive marker in prostate cancer, which is still debatable since other studies prove higher SHBG levels to be correlated with detection of prostate cancer[75]. Obesity has been shown to be significantly associated with prostate cancer stage and that low testosterone concentration is just a rising epiphenomenon of increased abdominal fat[76]. This might also have implications for interpretation of changing SHBG serum levels in this pathology. Adiposity, leading to liver steatosis as well as increased estrogen production, but coupled with the positive effects of estrogens and adiponectins on *SHBG* expression and negative effects of dysregulated cellular metabolism, chronic inflammation and androgen status on that same gene expression evidently describes a complex pathophysiological process where the role of SHBG as a mediator in hormonal transport and efficacy should be investigated further.

It had only been recently that SHBG has been considered to be investigated in relation to ovarian cancer. Its gene expression in cancerous cells was significantly correlated with cancer aggressiveness[77]. A smaller sample study[78] compared healthy and pathologically changed ovaries and concluded that premenopausal normal ovaries as well as cancerously changed both expressed *SHBG*, suggesting that a kept ability of the cancer to synthesize SHBG might be involved in cancerous growth. In addition, an overexpression in exon-7-splicing-variant of *SHBG* gene has been noted in ovarian cancerous cells when compared to healthy ones[79]. This exon is involved in coding the steroid binding site, so an alteration may have an impact in binding affinity for sex steroids, namely estrogen. The influence of SHBG in pathology of ovarian cancer and its clinical relevance still remains largely understudied.

Similarly, the connection of SHBG and endometrial cancer still remains to be investigated. An eight-year cohort study in European countries showed a correlation between lower SHBG plasma levels and appearance of endometrial cancer, but with inflammation having the prominent role in endometrial carcinogenesis[80]. Accordingly, SHBG might be substantially lowered due to ongoing inflammatory state. In a large gene-diet case control study, it has been shown that the consumption of soy and tea with a particular polymorphism in *SHBG* gene at Asp(327)/Asn(rs 6259) that prolongs SHBG half-life, which both leads to higher SHBG serum levels in pre-menopausal period and lower incidence of endometrial cancer in postmenopause[81]. It is also noted that as endometrial cancer undergoes de-differentiation, the levels of *SHBG* expression in endometrial cells decreases[82] accompanied by exon-7-splicing-variant increase[83]. Insofar, there isn't a clinical implication for SHBG as a marker in endometrial cancer and specifically orientated research is still scarce.

Insulin resistance in women and link with polycystic ovary syndrome (PCOS)

Insulin resistance is a common state associated with diseases already mentioned and strongly proven by systemic meta-analyses, these include obesity with predominant visceral fat[84], increased cardiovascular risk[85], endometrial cancer[86] and metabolic syndrome in which the presence of hyperglycemia is an including factor[46] for definition. Insulin resistance is also linked to polycystic ovary syndrome[87] and which is especially interesting from the view of assessing the role of SHBG as a mediator between the metabolism and hormonal status, i.e. reproductive health. With higher level of blood glucose, hepatic lipogenesis is promoted and a downregulation of HNF-4α follows, ultimately leading to lower production of SHBG[54]. Insulin does not in itself lower the hepatic production of SHBG[54] as was previously concluded in a common cited study for this claim[88], but it acts as a co-gonadotropic factor on the ovary exerting a negative effect on hormonal balance and signaling[89]. A hallmark of PCOS is androgenicity, which only aggravates the glucose regulation and also lowers the SHBG production thus having a double negative effect on the whole pathophysiological process by further promoting unfavorable metabolic changes and hormonal imbalance. When adiposity as a feature of metabolic syndrome is also co-present with PCOS, a state of chronic inflammation is also maintained and which further perpetuates the pathophysiological process of lowering SHBG levels and inducing other pathological process happening in PCOS. This is backed up by a meta-analysis showing connection of IL-6

levels and PCOS[90]. Treatments that include weight loss lowering insulin resistance through lifestyle modification[91,92] and combined with pharmacological treatment such as prescribing metformin[92], prove to be a successful approach in PCOS. Metformin alone or in combination with statins does alter the lipid profile and inflammation towards a more desirable status, but insulin sensitivity and hyperandrognicity doesn't reach a desirable therapeutic target[93], even though metformin induces a decrease of LH-stimulated testosterone response of the ovaries[94]. Oral contraception, which is also used in treating PCOS to regulate menstrual cycles and reduce androegnicity, raises HDL levels, but doesn't have a uniform effect regarding glucoregulation[95]. Exercise on its own has pleiotropic effects and is beneficial for women suffering from PCOS, since evidence exist that it produces positive changes in the metabolic profile[96], even when body weight doesn't decrease. Serum SHBG levels increase after lifestyle modification[97] in PCOS affected women.. The interrelations amid the different endocrine tissues are definitely emphasized in PCOS, mainly the gonads and the liver with peripheral metabolism-regulating tissues being the prominent 'headliners'. Sex hormones, insulin, adipokines are signal molecules that mediate their interplay. In regards to all these hormones having an effect on the liver, it being the site of most SHBG production, serum levels of SHBG will change in response to the predominant metabolic/hormonal state in an individual. From the molecular mechanisms explained earlier, comes the role of SHBG as both an actively involved protein in the pathophysiology, but being a valuable marker additionally.

Patients who responded to metformin therapy in PCOS had lower initial mean SHBG levels than those who did not[98,99]. In adolescent patients who had a more repeating TAAAA region in *SHBG* gene, a more beneficial effect on lipid profile was seen after one-year long treatment with metformin for PCOS[100], but *SHBG* gene and polymorphisms in their own aren't associated with PCOS in etiological sense[101]. After adjustment for fasting insulin levels, fasting glucose and adipokines in mixed population, low SHBG remained a strong marker in women for dysregulated glucose metabolism, independently of the aforementioned values and could serve as an identifying factor for developing diabetes[102]. Increased liver fat in midlife women with a higher metabolic risk showed a strong independent connection with low SHBG levels[51]. In women of fertile age that were in treatment for PCOS with goals of reaching ovulation, pregnancy and birth, increased SHBG and decreased free-androgen index strongly marked the effectiveness of the treatment[103]. There is even evidence that preconception SHBG levels in women affected with PCOS may be a better predictor for development of gestational diabetes mellitus than waist circumference or insulin resistance (HOMA-IR)[104]. In a study on 180 women, for each increment of a single unit of nanomol per liter, there was a 7% reduction in the risk for development of gestational diabetes mellitus[105].

With clarification of the exact pathophysiology and reasons for the changing levels of SHBG, i.e. defining what is the cause and what is the consequence, surely a more specific role for this protein as a marker could be implemented. For now, the mentioned uses might be considered reliable.

Osteoporosis

Bone helath is inevitably associated with sex hormones and thusly with SHBG as the main carrier-protein. In a longitudinal study on more than 6 000 women that lasted for almost 20 years, it was observed that lower ratio of androgens and SHBG correlated with osteoporotic fractures[106], while the opposite being true for a higher ratio. Elderly men have lower free testosterone and higher SHBG levels, which was associated with lower bone mineral density[107] and vertebral fractures[108-110], it is important to keep in mind the fact that male SHBG tends to increase with age[5]. Generally, higher levels of SHBG in both sexes were associated with greater bone resorption and lower bone mineral density[109,111,112], predisposing one for osteoporotic fractures. Increased levels of unbound sex hormones might be beneficial for prevention of osteoporosis[113], suggesting that high SHBG levels in older population are undesirable regarding bone helath.

Conclusion

SHBG is an important protein since its involved in regulating sex hormone availability, but also possess an ability to influence the effect of the hormone when it bind to the receptor, the reason being the existence of SHBG-R. This review demonstrated the various pathophysiological roles of this protein, but also diseases where it can clini-

TABLE 1
SEX HORMONE BINDING GLOBULIN: AN OVERVIEW OF PATHOPHYSIOLOGY AND CLINICAL USES

Causes of higher serum levels of sex hormone binding globulin	Thyroid hormones Estrogens Adiponectins ß-oxidation in producing cells Oleic acid intake
Causes of lower serum levels of sex hormone binding globulin	Inflammation Fatty liver Androgens
Current states where sex hormone binding globulin can be used as a marker	Anorexia nervosa Obesity Low serum HDL Breast and prostate cancer Gestational diabetes mellitus, Polycystic ovary syndrome Osteoporosis
Possible future implications where sex hormone binding globulin could be used as a marker	Infertility Aging Neurodegenerative diseases

cally help in marking certain outcomes or present states in which an individual currently is. A brief overview of pathophysiological processes affecting SHBG levels, its current clinical use and possible future implications are represented clearly in Table 1. Future research should bring interesting findings, since possibilities for using SHBG as a marker are numerous, but it also warrants thorough comprehension of its physiology, an area which is still understudied. Additionally, possible links with the hormone oxytocin could yield important implications, while the focus is still on its primary role of binding sex hormones. The existence of SHBG-R also implies that the 'free-hormone-hypothesis' shouldn't be misused, and by investigating the physiology of these receptors, more accurate and correct findings are bound to come.

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M. Š. Goldštajn

University of Zagreb, School of Medicine, Department for Gynecology and Obstetrics, KBC Zagreb, Petrova 13, Zagreb

GLOBULIN KOJI VEŽE SPOLNE HORMONE (SHBG) KAO MARKER U KLINIČKIM POREMEĆAJIMA

S A Ž E T A K

Globulin koji veže spolne hormone (SHBG) je važan protein, ne samo kao primarni nosač spolnih steroida, nego se i otkrićem specifičnog receptora koji veže SHBG treba usvojiti novi pristup klasičnoj teoriji 'slobodnih hormona'. Istražen je gen *SHBG*, kao i stanični mehanizmi koji utječu na njegovu ekspresiju. Značajna saznanja su dobivena i postoje dobro objašnjeni signalni putevi na staničnoj razini koji utječu na proizvodnju SHBG. Štoviše, pokazano je da SHBG nije samo periferno sintetiziran protein, već je njegovo postojanje potvrđeno i u moždanom tkivu, u području hipotalamusa i hipofize. Ovdje je prostorno razmješten u bliskosti s neuronima koji proizvode oksitocin. Glavni periferni organ koji proizvodi SHBG jesu jetra. Budući da su jetra središnji metabolički organ, određene metaboličke bolesti će rezultirati promijenjenom razinom SHBG u krvi. S druge strane, endokrinološki poremećaji tkiva uključenih u regulaciju spolnih hormona također će imati utjecaj na razinu SHBG. Stoga, SHBG stoji kao jedan od posrednika između različitih endokrinološki aktivnih tkiva i definitivno pridonosi svojom patofiziološkom ulogom u bolestima poput: debljine, metaboličkog sindroma, sindroma policističnih ovarija, osteoporoze, raka dojke i raka prostate. Njegova vrijednost prelazi i u područje kliničke medicine kao biljega određenih patoloških stanja. Neke studije su već utvrdile njegovu pouzdanost i postoji rastući trend da se uvede kao korisni biljeg u kliničkoj medicini. U pogledu patofiziologije i kliničke medicine, još uvijek nije dovoljno proučen, ali nedavni pronalasci daju naznake da SHBG ima važnu ulogu u zdravlju i bolesti i mogao bi predstavljati koristan biljeg za procjenu u kliničkoj medicini.