Original Article

Sex Hormone Binding Globulin (SHBG) - A Potential Biomarker for Insulin Resistance, Non-Alcoholic Fatty Liver and Hepatic Lipogenesis

Priya Alva
Tutor, Department of Biochemistry, K S Hegde Medical Academy, NITTE (Deemed to be University)..
Email: drpriya.alva@nitte.edu.in

DOI: 10.47750/pnr.2022.13.S07.710

Abstract

The liver produces and secretes sex hormone-binding globulin (SHBG), which binds to sex steroids and controls their bioavailability in the bloodstream. Recent research indicates that, insulin resistance, liver fat content, hepatic lipogenesis is a significant predictor of circulating SHBG. In this review we discuss the role of SHBG as a potential biomarker that may lead to new diagnostic and therapeutic methods.

INTRODUCTION

Sex Hormone-Binding Globulin (SHBG) was discovered and isolated for the first time in 1965 by Mercier-Bodard and colleagues in France[1]. In biological fluids, SHBG is mainly synthesized in the liver[2]. SHBG mRNA is also expressed in other tissues including testis[3], prostrate[4] hypothalamus[5], ovary[6], placenta [7], endometrium breast[8], and cardiac myocytes[9] SHBG exists as a homo-dimer with 373 amino acid residues. It consists of G-like (LG) domain in tandem repeats at the N-terminal end which consists of antiparallel β –sheets on top of each other[10]. The transport and distribution of steroids is significantly impacted by their binding to SHBG[11]. In plasma, hydrophobic sex hormones link to hydrophobic sites on the proteins that bind the lipophilic cellular membrane to the hydrophilic aqueous extracellular fluid. SHBG has a strong preference for testosterone and a weak preference for estradiol. Dihydrotestosterone (DHT) > testosterone > androstenediol > estradiol > estrone is the order of the major sex steroids' relative binding affinities for SHBG[12]. Only 1-2% of the testosterone in circulation is free (unbound) and active; 65% of it is bound to SHBG, and the remaining portion is bound to albumin[13]. As a result, the concentrations of SHBG have a significant impact on the levels of free active testosterone in plasma. Consequently, women with low SHBG may have normal total testosterone levels but higher amounts of free and bioavailable testosterone[14]. Cross-sectional studies suggest that SHBG levels significantly increase from birth through early childhood and subsequently fall at puberty, more so in males than in girls, likely as a result of androgens, which are known to inhibit SHBG levels[15], [16]. Since the liver is primarily responsible for secreting SHBG into the bloodstream, a greater understanding of how SHBG is expressed in the liver may lead to new diagnostic and therapeutic methods.

Monosaccharides (glucose or fructose), insulin, and androgens negatively influence the production of SHBG, according to a study employing a human hepatoma cell line (HepG2)[17]. The two most effective transcriptional factors (TP) involved in the control of SHBG expression are HNF-4 and PPAR. Numerous studies therefore showed that an increase in de novo lipogenesis caused HNF-4 levels to fall and PPAR levels to rise, which in turn reduced the generation of SHBG[18]. Studies demonstrated that thyroid, estrogenic, and phytoestrogen hormones stimulate SHBG production by up-regulating HNF-4α expression[19, 20] . SHBG serves as a hormone or signal transduction factor, in addition to serving as a protein that binds to other sex hormones like as testosterone, estradiol, and others. The PI3K/AKT pathway, which is involved in the onset of both local and systemic insulin resistance, may be down-regulated by SHBG, according to in vitro studies using cellular models of human insulin resistance that showed decreased expression of SHBG protein and mRNA levels, along with decreased levels of IRS-1, IRS-2, PI3Kp85a, GLUT-3, and GLUT-4 mRNA and protein levels[21]. Overexpression of SHBG protects against high fat diet (HFD) induced obesity and insulin resistance, as demonstrated by lower glucose profiles during glucose tolerance tests and insulin tolerance tests, according to an in vivo animal investigation utilising

SHBG transgenic mice compared with wild type mice[22]. According to the Study of Women's Health Across the Nation (SWAN), women with fatty livers also had a negative relationship between SHBG and insulin. In addition, greater liver fat and lower SHBG were linked to increased metabolic risk in midlife[23].

SHBG and non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver is characterized by an increase in hepatic triglyceride content with or without inflammation[25]. NAFLD is associated with clinical states such as obesity, insulin resistance, and T2DM [26, 27]. Lipogenesis is one of the factors that drive fat accumulation in the liver but apart from that evidence supports a central role of SHBG in the development of NAFLD. Most recently by using the model of human SHBG transgenic mouse has shown that SHBG modulates hepatic lipogenesis and how the reduction of SHBG expression is associated with NAFLD development through an increase in hepatic lipogenesis [28]. This data showed that there are normal SHBG levels in a healthy liver that determine lipogenic rate by regulating PPARϒ through ERK1/2 MAPK pathway [28]. This lipogenesis determines and maintains the SHBG level by regulating HNF4-α and PPARϒ transcription factor. During the development of NAFLD, elevated cytokines and both genetic and nutritional factors reduce SHBG levels that decrease the signalling through the ERK1/2 MAPK pathway, increasing PPARϒ lipogenesis. The increase in lipogenesis reduces the level of SHBG by downregulating HNF4-α resulting in a process of fat accumulation and decrease SHBG production.

Hepatic Denovo lipogenesis and SHBG

The increased hepatic lipogenesis in insulin resistant states inhibits the expression of HNF-4α, thus down-regulating SHBG gene transcription and SHBG production. Increased Denovo lipogenesis induced by elevated concentration of monosaccharide's decreases the production of HNF4-α, a key transcriptional factor that regulates the production of SHBG. Thus data suggest that HNF4-α is an important transcriptional factor that activates SHBG production whereas PPARϒ is an inhibitor of SHBG expression, [29]. Therefore SHBG is highly indicative of denovolipogenesis. A study employing liver samples from non-diabetic obese patients with NAFLD showed that triglycerides accumulate in the liver and that insulin resistance (measured by the homeostasis model assessment, HOMA-IR) was inversely associated to SHBG.

Metabolic syndrome is associated with adipocyte insulin resistance that induces lipid deposition resulting in lipotoxicity. Non esterified fatty acids released during lipolysis inhibit HNF4-α with the decreased concentration of SHBG production. In addition, tumor necrosis factor (TNF), an inflammatory cytokine generated from adipose tissue, can affect hepatic insulin signalling and encourage the formation of intrahepatic triglycerides, which inhibits the expression of HNF-4 α through activating nuclear factor-Kb[29.]

Conclusion

Our understanding of the regulation of SHBG and its clinical consequences has undergone a transformation as a result of the unique discoveries from fundamental research and clinical pilot trials. A decrease in the SHBG levels is observed in association with Inflammation, T2D, hepatic lipogenesis, NAFLD. Future studies are required to understand the underlying molecular mechanisms behind this association and to investigate the possible therapeutic effects of SHBG.

REFERENCES

1. Mercier C, Alfsen A, Baulieu EE. A testosterone binding globulin. In Proceedings of the second symposium on the steroid hormones. Ghent ed. Excerta Medica International Congress Series 1966.
2. Hammond GL, Underhill DA, Smith CL, Goping IS, Harley MJ, Musto NA, Cheng CY, Bardin CW. The cDNA-deduced primary structure of human sex hormone-binding globulin and location of its steroid-binding domain. FEBS letters. 1987 May 4;215(1):100-4.
3. Selva, D.M. and G.L. Hammond, Human sex hormone-binding globulin is expressed in testicular germ cells and not in sertoli cells. Horm Metab Res, 2006. 38(4): p. 230-5.
4. Hryb, D.J., et al., Sex hormone-binding globulin in the human prostate is locally synthesized and may act as an autocrine/paracrine effector. J Biol Chem, 2002. 277(29): p. 26618-22.
5. Herbert, Z., et al., Identification of sex hormone-binding globulin in the human hypothalamus. Neuroendocrinology, 2005. 81(5): p. 287-93)
6. Forges, T., et al., Expression of sex hormone-binding globulin (SHBG) in human granulosa-lutein cells. Mol

Cell Endocrinol, 2004. 219(1-2): p. 61-8.
7. Hammond, G.L., Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. J Endocrinol, 2016. 230(1): p. R13-25.).
8. Larrea, F., et al., Evidence that human placenta is a site of sex hormone-binding globulin gene expression. J Steroid Biochem Mol Biol, 1993. 46(4): p. 497-505.
9. Fortunati, N., et al., Sex Hormone-Binding Globulin (SHBG), estradiol and breast cancer. Mol Cell Endocrinol, 2010. 316(1): p. 86-92.
10. Schock, H.W., et al., Expression of androgen-binding protein (ABP) in human cardiac myocytes. Horm Metab Res, 2006. 38(4): p. 225-9.
11. Avvakumov Gv, Cherkasov A, Muller Ya, Hammond Gl. Structural Analyses Of Sex Hormone-Binding Globulin Reveal Novel Ligands And Function. Molecular And Cellular Endocrinology. 2010; 5;316(1):13-23.)
12. Dunn, J.F.; Nisula, B.C.; Rodbard, D. Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J. Clin. Endocrinol. Metab. 1981, 53, 58–68.
13. Zakharov MN, Bhasin S, Travison TG, Xue R, Ulloor J, Vasan RS, Carter E, Wu F, Jasuja R. A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. Molecular and cellular endocrinology. 2015 Jan 5;399:190-200
14. Karakas, S.E. New biomarkers for diagnosis and management of polycystic ovary syndrome. Clin. Chim. Acta 2017, 471, 248–253)
15. Elmlinger, M.W.; Kühnel, W.; Wormstall, H.; Döller, P.C. Reference intervals for testosterone, androstenedione and SHBG levels in healthy females and males from birth until old age. Clin. Lab. 2005, 51, 625–632
16. Garcés, C.; Oya, I.; Lasunción, M.A.; López-Simón, L.; Cano, B.; de Oya, M. Sex hormone-binding globulin and lipid profile in pubertal children. Metabolism 2010, 59, 166–171.
17. Selva, D.M.; Hogeveen, K.N.; Innis, S.M.; Hammond, G.L. Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene. J. Clin. Investig. 2007, 117, 3979–3987.
18. Simó R, Sáez-López C, Barbosa-Desongles A, Hernández C, Selva DM. Novel insights in SHBG regulation and clinical implications. Trends in Endocrinology & Metabolism. 2015
19. Selva, D.M.; Hammond, G.L. Thyroid hormones act indirectly to increase sex hormone-binding globulin production by liver via hepatocyte nuclear factor-4alpha. J. Mol. Endocrinol. 2009, 43, 19–27.
20. Pugeat, M.; Nader, N.; Hogeveen, K.; Raverot, G.; Déchaud, H.; Grenot, C. Sex hormone-binding globulin gene expression in the liver: Drugs and the metabolic syndrome. Mol. Cell Endocrinol. 2010,
21. Feng, C.; Jin, Z.; Chi, X.; Zhang, B.; Wang, X.; Sun, L.; Fan, J.; Sun, Q.; Zhang, X. SHBG expression is correlated with PI3K/AKT pathway activity in a cellular model of human insulin resistance. Gynecol. Endocrinol. 2018, 34, 567–573.)
22. Saez-Lopez, C.; Villena, J.A.; Simó, R.; Selva, D.M. Sex hormone-binding globulin overexpression protects against high fat diet induced obesity in transgenic male mice. J. Nutr. Biochem. 2020, 85, 108480.
23. Kavanagh, K.; Espeland, M.A.; Sutton-Tyrrell, K.; Barinas-Mitchell, E.; El Khoudary, S.R.; Wildman, R.P. Liver fat and SHBG affect insulin resistance in midlife women: The Study of Women's Health Across the Nation (SWAN). Obesity 2013, 21, 1031–1038).
24. Kitade H, Chen G, Ni Y, Ota T. Nonalcoholic fatty liver disease and insulin resistance: new insights and potential new treatments. Nutrients. 2017 Apr;9(4):38
25. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nature medicine. 2018 Jul;24(7):908-22.
26. Lindenmeyer CC, McCullough AJ. The natural history of nonalcoholic fatty liver disease—an evolving view. Clinics in liver disease. 2018 Feb 1;22(1):11-21.
27. Saez-Lopez C, Barbosa-Desongles A, Hernandez C, Dyer RA, Innis SM, Simó R, Selva DM. Sex hormone-binding globulin reduction in metabolic disorders may play a role in NAFLD development. Endocrinology. 2017 Mar 1;158(3):545-59.
28. Simó R, Barbosa-Desongles A, Hernandez C, Selva DM. IL1β down-regulation of sex hormone-binding globulin production by decreasing HNF-4α via MEK-1/2 and JNK MAPK pathways. Molecular

Endocrinology. 2012 Nov 1;26(11):1917-27.

29. Longo, M.; Zatterale, F.; Naderi, J.; Parrillo, L.; Formisano, P.; Raciti, G.A.; Beguinot, F.; Miele, C. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int. J. Mol. Sci. 2019, 20, 2358.