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The biomarker sex hormone-binding globulin – From established applications to emerging trends in clinical medicine

Markus A. Thaler, MD, Dr. Med. [a, 1],
Vanadin Seifert-Klauss, MD, Priv.-Doz. Dr. Med. [b, 2],
Peter B. Luppa, MD, Prof. Dr. Med. [a, *]

[a] *Institut für Klinische Chemie und Pathobiochemie, Klinikum rechts der Isar der TU München, Ismaninger Str. 22, 81675 München, Germany*
[b] *Frauenklinik und Poliklinik, Klinikum rechts der Isar der TU München, Ismaninger Str. 22, 81675 München, Germany*

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Sex hormone-binding globulin (SHBG) is a serum glycoprotein exhibiting the unique feature of binding sex steroids with high affinity and specificity. Its serum levels are regulated not only by androgens and estrogens but also by thyroid hormones and other metabolic factors. Several disease conditions are accompanied by altered SHBG levels such as hyper- and hypoandrogenism, thyroid disorders, pituitary diseases, liver disorders, and breast as well as prostate cancer. Additionally, several drugs and alcohol consumption influence serum concentrations of SHBG. In some cases, altered SHBG levels are a specific result of the underlying pathology. In others, they merely constitute an epiphenomenon, which still might offer the possibility of using serum measurements of SHBG as surrogate marker. This review article portrays the different disorders associated with altered SHBG levels and discusses the usefulness of SHBG as disease biomarker from a clinicians as well as from an endocrinological researchers point of view.

* Corresponding author. Tel.: +49 89 4140 4759; Fax: +49 89 4140 4875.
E-mail addresses: thaler@klinchem.med.tum.de (M.A. Thaler), Vanadin.Seifert-Klauss@lrz.tu-muenchen.de (V. Seifert-Klauss), luppa@klinchem.med.tum.de (P.B. Luppa).
[1] Tel.: +49 89 4140 5056; Fax: +49 89 4140 4875.
[2] Tel.: +49 89 4140 5434; Fax: +49 89 4140 6757.

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Abbreviations

BMI	body-mass-index
BRCA	breast cancer
COC	combination oral contraceptives
DHT	dihydrotestosterone
E2	estradiol
FSH	follicle stimulating hormone
HCC	hepatocellular carcinoma
HNF-4α	hepatocyte nuclear factor-4α
IGF-1	insulin like growth factor-1
LEIAED	liver enzyme inducing antiepileptic drugs
LGLD	laminin G-like domain
LH	luteinizing hormone
METS	metabolic syndrome
PCOS	polycystic ovary syndrome
PRCA	prostate cancer
SHBG	human sex hormone-binding globulin
T	testosterone
T2DM	type 2 diabetes mellitus
WHR	waist-to-hip ratio

Introduction

Human sex hormone-binding globulin (SHBG) is a serum protein that binds androgens and estrogens with high affinity and specificity. It is synthesized in the liver and secreted into the circulation, where it can be found in the serum β–globulin fraction. SHBG serum levels are primarily regulated by sex hormones but also influenced by several other hormones and non-hormonal factors. As a consequence, altered SHBG concentrations can be found in a multitude of physiological and pathological conditions ranging from pregnancy over sex steroid and pituitary disorders to the metabolic syndrome (METS) and cardiovascular diseases.

The following review starts with a brief overview on the biochemical features of this steroid-binding protein and its biological importance. Subsequently, disorders with altered SHBG serum levels are described in detail; the usefulness of SHBG determination is discussed respectively. The aim of the article is to provide the reader with the necessary information to judge whether measurements of SHBG serum concentrations as biomarker are beneficial or can be omitted without serious drawbacks for a given endocrine or research situation.

Molecular structure of SHBG

Native SHBG is a homodimeric glycoprotein with a molecular weight of approximately 90 kDa. Each monomer consists of 373 amino acids and exhibits two intramolecular disulfide bridges. Two biantennary N-linked oligosaccharides and one O-linked oligosaccharide are attached to each monomer [1]. The tertiary structure of a monomer is characterized by a carboxy-terminal laminin G-like domain (LGLD), which is joined to an amino-terminal LGLD by a short linker region. The amino-terminal LGLD is comprised of two seven-stranded antiparallel β-sheets on top of each other [2]. Due to their high affinity, SHBG monomers spontaneously dimerize during synthesis and secretion and are solely found as dimer in blood. Dimerization takes place in between the N-terminal LGLD of the involved monomers in a head-to-head manner (Fig. 1). Eight hydrogen bonds are formed across the interface of the β-sheets leading to two continuous 14-stranded β-sheets and an elongated, cylindric shape of the mature dimer