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Sex Hormone Binding Globulin and the Assessment of Androgen Status

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Sex Hormone Binding Globulin and the Assessment of Androgen Status

Unconjugated steroids in the blood exist mostly in noncovalently bound complexes with carrier proteins; less than two percent of unconjugated steroids circulate in the unbound form. Given that free steroids readily enter cells and are physiologically active, various regulatory systems strictly control the size of the unbound hormone fraction. Carrier proteins such as sex hormone binding globulin (SHBG) have important roles in regulating the amount of unbound steroid in the blood. SHBG's impact on steroid-mediated processes has attracted increasing attention. Various physiological conditions cause shifts in the circulating levels of this high-affinity steroid-binding protein, and serum measurements can indicate several androgen abnormalities.

Binding Characteristics

SHBG, also known as testosterone-estrogen binding globulin (TeBG), sex steroid binding globulin (SSBG), or sex steroid binding protein (SBP), specifically binds 17β-hydroxysteroids in a 1:1 ratio. The glycosylated heterodimer (80 to 100 kDa) binds 5α-dihydrotestosterone (DHT) most tightly, followed by testosterone and estradiol.[1] (See Table 1)

SHBG in Healthy Subjects

SHBG is synthesized by liver cells and has a 7- day half-life in circulation. In both sexes the SHBG concentration sharply increases just after birth and gradually declines until puberty. Male and female children have similar SHBG concentrations (ranging from 80 to 175 nmol/L) until the onset of puberty, when SHBG levels decrease more rapidly in males than in females.[2] Table 2 shows average SHBG levels for healthy adults. In pregnant women, the SHBG level increases from conception until about week 30, reaching concentrations 6 to 10 times higher than in nonpregnant females.

The circulating androgen concentration affects SHBG synthesis. Elevated testosterone causes SHBG synthesis to decrease, while high estrogen stimulates SHBG production. The regulation of SHBG synthesis, combined with SHBG's high affinity for testosterone compared to estrogen, results in SHBG effectively amplifying the estrogen level.

Table 1: SHBG equilibrium constants at 37°C[1]

Steroid	K (x $10^9 M^{-1}$)
5α-Dihydrotestosterone (DHT)	5.5
Testosterone	1.6
Androstenediol	1.5
Estradiol	0.68
Estrone	0.15
Dehydroepiandrosterone (DHEA)	0.066
Progesterone	0.009

Table 2: SHBG concentration in healthy adults

	n	Median (nmol/L)	Central 95%
Males	122	32	13 – 71
Females*	111	51	18 – 114

*Nonpregnant

SHBG In Disease States

Levels of testosterone and estradiol in circulation influence SHBG production, and SHBG measurements not only indicate the amount of unbound steroid available to tissues, but also the post-receptor cellular response to androgen and estrogen levels. Because SHBG responds to circulating estrogen and testosterone levels, SHBG measurements can indicate a range of androgen abnormalities. Table 3 lists various pathological conditions that involve abnormal SHBG levels.

SHBG levels respond to extreme changes in body weight, decreasing in obese patients and increasing in females with anorexia nervosa.[3,4] Females with hyperprolactinemia often have low SHBG levels. Human growth hormone and prolactin are evolutionarily related, and SHBG levels are similarly low in acromegaly and patients receiving growth hormone treatments. The SHBG level is likely to be abnormal in male hypogonadism, androgen insensitivity, thyroid disorders, diabetes mellitus, and liver disease.[5]

Table 3: SHBG levels in disease states

Elevated	Suppressed
Anorexia nervosa	Obesity
Hyperthyroidism	Hypothyroidism
Hypogonadism (males)	Hirsutism (females)
Androgen insensitivity/deficiency	Acne vulgaris
Alcoholic hepatic cirrhosis (males)	Polycystic ovarian disease
Primary biliary cirrhosis (females)	Acromegaly
	Androgen-secreting ovarian tumors

Role As A Carrier Protein

Although the precise role of SHBG and other hormone carriers in steroid regulation and metabolism remains unclear, several theories propose that the proteins function as hormone reservoirs to modulate fluctuations in steroid concentrations. The presence of carrier proteins in the blood influences the dynamic equilibrium that exists between bound and free steroid fractions and modifies the amount of steroid available to cells. Several factors affect the equilibrium, including the concentrations of carrier proteins, carrier protein binding affinities, the total specific steroid concentration, and concentrations of steroids that compete for the carrier protein binding sites. Efforts to quantify the amount of a particular steroid circulating in an active form must include information on carrier protein status as well.

Hormone carriers exist predominantly in the unbound form, providing a large excess of unfilled steroid binding sites. Over 80% of the SHBG population is unbound in females and over 40% is unbound in males. The other principle testosterone and estrogen carrier, albumin, circulates unbound 99% of the time.[6] Changes in the total hormone concentration produce relatively minor changes in the size of the free fraction because excess carrier protein binding sites modulate extreme variations in hormone concentrations.

In contrast, changes in the SHBG concentration greatly affect the amount of steroid available to tissues. SHBG binds testosterone with high affinity, and changes in the SHBG concentration result in large shifts in the free and albumin-bound testosterone fractions. Since albumin's steroid affinity is low (on the order of 10-4 mol/L), the albumin-bound testosterone fraction may be considered "bioavailable," or able to diffuse into cells.[7] The circulating SHBG concentration impacts the bioavailable testosterone level.

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Effect on the Free Testosterone Level

SHBG greatly influences the bioavailable testosterone level because it binds with high affinity to a large fraction of the testosterone in circulation (Table 4). Albumin binds a high percentage of the testosterone with low affinity, and another hormone carrier protein, cortisol binding globulin, binds with low affinity to less than 1% of the testosterone population.

Total testosterone may fluctuate in concert with SHBG to maintain a relatively constant free testosterone concentration. Total testosterone measurements, in the absence of SHBG measurements, are difficult to interpret. Decreased SHBG, concomitant with normal to just slightly elevated total testosterone, results in greater peripheral androgen activity, as seen in disorders such as hirsutism, severe acne, virilism, and features of polycystic ovarian disease.[5,8] Management of these diseases often involves either suppressing androgen synthesis or stimulating SHBG synthesis via estrogen supplements.

Table 4: Testosterone in circulation

Carrier Protein	%Total Testosterone	
	Females	Males
None (Free)	0.01 - 3.0	0.16 - 0.68
Albumin	25 - 65	45 - 85
SHBG	35 - 75	14 - 50

Results are based on a Siemens study conducted on healthy adults age 20 and over (81 females, 87 males).

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Free Androgen Index

The concentration of total testosterone (TT) divided by the concentration (or binding capacity) of SHBG, provides a sensitive measure of androgen status. The molar ratio, called the "Free Androgen Index" (FAI), is given by.

$$FAI = \frac{[TT\ (nmol/L)]}{[SHBG\ (nmol/L)]}$$

FAI indicates the amount of bioavailable testosterone and helps to assess specific androgen abnormalities. When the SHBG level is low and total testosterone remains normal or slightly elevated, a patient's FAI can accurately distinguish androgen status. Several diseases show no increase in total testosterone, but have higher than normal FAI scores. These include male androgenic alopecia (balding), hirsutism, and severe acne.[9]

In clinical pathologies where changes in SHBG levels are likely to occur, total testosterone measurements must be accompanied by SHBG tests in order to knowledgeably assess peripheral androgen activity. The IMMULITE® and ADVIA Centaur® Systems from Siemens provide both Total Testosterone and SHBG assays.

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