



Kaiser Foundation Health Plan of Washington

Clinical Review Criteria Sex-Hormone Binding Globulin (SHBG)

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Criteria For Medicare and Non-Medicare Members

Medical necessity review no longer required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Causes of abnormal SHBG include the following:

- Increased SHBG concentrations: aging, hyperthyroidism, high estrogen concentrations, liver disease, HIV, anti-seizure drugs
- Decreased SHBG concentrations: moderate obesity, insulin resistance, type 2 diabetes, hypothyroidism, growth hormone excess, exogenous androgens/anabolic steroids, glucocorticoids, progestins, nephrotic syndrome
- Free testosterone — If serum free testosterone concentration is measured, the following points should be kept in mind:
 - Serum free testosterone should be performed by equilibrium dialysis and only in those few laboratories that specialize in endocrine testing.
 - The free testosterone concentration, as calculated from the total testosterone, SHBG, and albumin concentrations, may also be reliable, but there are many different equations for this calculation and they give vastly different results, some of which reflect the results obtained by equilibrium dialysis better than others. Consequently, it is essential that the result be compared with the normal range for the laboratory that performed the assay.
 - Free testosterone measured by an analog method, which is the assay most commonly offered by hospital and commercial laboratories, does not correlate with the results of equilibrium dialysis. This test gives misleading information and should never be ordered.
 - The problem with the analog method was illustrated in a study in which sera from patients who had a variety of SHBG concentrations were assayed by each of the above methods. The results using each of the assays correlated well with the results using each of the other methods, except for free testosterone by the analog method, in which the results were both systematically lower than in the other methods and varied as a function of SHBG.
 - Bioavailable testosterone, ie, the total of free testosterone and that bound weakly to albumin, which is not precipitated by ammonium sulfate, also appears to accurately reflect androgen status.

When during the day should the serum testosterone concentration be measured? — Interpretation of serum testosterone measurements in young men should take into consideration its diurnal fluctuation, which reaches a maximum at about 8 AM and a minimum, approximately 70 percent of the maximum, at about 8 PM. It is easier to distinguish subnormal from normal when normal is higher, so the measurements should always be made in the

morning, ideally between 8 to 10 AM. Food, especially glucose ingestion, also decreases the serum testosterone concentration, so the blood should also be drawn fasting.

How often should testosterone be measured? — The serum testosterone concentration fluctuates somewhat even early in the morning, although to a limited degree. If a single 8 to 10 AM value is well within the normal range, testosterone production can be assumed to be normal. If a single 8 to 10 AM value is low or borderline low or does not fit with the clinical findings, the measurement should be repeated once or twice before making the diagnosis of hypogonadism. If the results are equivocal, measurement of free testosterone can be considered.

Sex hormone-binding globulin (SHBG) is a serum protein that binds to circulating androgens and estrogens, specifically testosterone and estradiol, with high affinity and serves as a transporter/reservoir. It is believed that SHBG regulates the access and action of these hormones. Initially it was thought that when bound to SHBG these sex hormones were biologically inactive. However, emerging evidence suggests that even sex hormones bound to SHBG may be biologically active. SHBG is produced mainly in the liver; however, other tissues including the placenta, testis, brain, and endometrium also produce SHBG. Age and obesity along with a variety of hormonal, nutritional, metabolic, and genetic factors have been found to influence the production of SHBG. Several conditions such as diabetes, polycystic ovarian syndrome, obesity, hypothyroidism, and hyperinsulinemia are associated with low levels of SHBG; however, causality has yet to be proven. Because of SHBG association with type 2 diabetes, there has been growing interest in the use of SHBG levels as a tool for the early identification of this disease (Brand 2010, Dahan 2006, Hoppé 2010, Xita 2010).

Medical Technology Assessment Committee (MTAC)

Sex-Hormone Binding Globulin

02/14/2011: MTAC REVIEW

Evidence Conclusion: *Men:* Two prospective cohort studies evaluated the association between SHBG levels and the risk of type 2 diabetes in men. The first study followed 1,454 men from the Troms study, a population-based prospective cohort study, who did not have diabetes at baseline for a mean of 9.1 years. Seventy-six men were diagnosed with diabetes (incidence rate of 5.8 per 1,000 person years). After controlling for age, HDL-cholesterol, systolic blood pressure, and waist circumference there was no association between SHBG and the risk of diabetes (Vikan 2010). The second study followed 1,128 men aged 40-70 years who participated in the Massachusetts Male Aging Study, a population-based prospective cohort study, for an average of 13 years. Ninety men were diagnosed with diabetes (incidence rate of 6.2 per 1,000 person years). Results from this analysis suggest that in men, even after controlling for age, BMI, high blood pressure, smoking, alcohol intake, and physical activity, SHBG levels were associated with the development of type 2 diabetes (Laksham 2010). It should be noted that the mean levels of SHBG were higher in the Vikan study compared to the Laksham study (52.7 nmol/l vs. 32.0 nmol/l). This may be due to the fact that blood sample were drawn at different times of the day. Diabetes status was determined through self-report in both studies. Additionally, neither study adjusted for insulin levels, which have been found to inhibit SHBG production. An earlier systematic review and meta-analysis of 3 prospective cohort studies found that men with higher SHBG levels (>28.3 vs. ≤28.3 nmol/l) had a 52% lower risk of type 2 diabetes (RR 0.48, 95%CI 0.33-0.69) (Ding 2006). *Women:* One prospective cohort study was identified that evaluated the association between SHBG levels and the risk of type 2 diabetes in postmenopausal women. In this study, 1,612 women were followed for a median of 4.7 years and 116 women were diagnosed with diabetes. Results from this study suggest that in postmenopausal women SHBG levels are associated with the development of type 2 diabetes even after adjusting for age, race/ethnicity, education, income, family history of diabetes, examination site, insulin resistance, and adiposity.

Relative hazards of developing incident type 2 diabetes by quartile of baseline SHBG level

	Model 1*	Model 2†	Model 3‡
	HR (95% CI)		
SHBG (nmol/l)			
Q1 (8.9-37.8)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Q2 (38.0-51.4)	0.39 (0.25-0.61)	0.49 (0.31-0.76)	0.41 (0.24-0.69)
Q3 (51.5-71.5)	0.29 (0.18-0.47)	0.44 (0.26-0.74)	0.53 (0.30-0.92)
Q4 (71.8-255.5)	0.24 (0.14-0.42)	0.43 (0.24-0.76)	0.52 (0.27-0.98)
P-trend	<0.0001	0.0004	0.017

*Adjusted for age, race/ethnicity, education, income, family history of diabetes, and examination site.

†Adjusted for model 1 plus BMI and homeostasis model assessment of insulin resistance (HOMA-IR).

‡Adjusted for model 2 plus LDL, HDL, triglycerides, use of lipid-lowering medication, systolic blood pressure, total daily caloric intake, physical activity, smoking, inflammatory factors (IL-6 and CRP), age at menopause, years since menopause, type of menopause, age at first live birth, five or more live births, past use of hormone replacement therapy or oral contraceptive.

An earlier systematic review and meta-analysis of 2 prospective cohort studies found that women with higher SHBG levels (>60.0 vs. ≤60.0nmol/l) had an 80% lower risk of type 2 diabetes (RR 0.20, 95%CI 0.12-0.30) (Ding 2006). Conclusion: Several observational studies suggest that lower SHBG levels are associated with an increased risk of developing of type 2 diabetes; however, SHBG cut points for determining increased risk have not been established. Additionally, there is insufficient evidence to determine the clinical utility of using SHBG to predict type 2 diabetes.

Articles: The literature search revealed several case-control, cross-sectional, and prospective cohort studies that examined the association between SHBG and the risk of type 2 diabetes. Three recent prospective cohort studies were selected for review. No studies were identified that addressed the clinical utility of using SHBG to predict type 2 diabetes. The following studies were critically appraised: Kalyani RR, Franco M, Dobs AS, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. *J Clin Endocrinol Metab* 2009; 94:4127-4135. See [Evidence Table](#). Lakshman KM, Bhasin S, and Araujo AB. Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes in men. *J Gerontol a Biol Sci Med Sci* 2010; 65A: 503-509. See [Evidence Table](#). Vikan T, Schirmer H, Njolstad I, and Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. *Eur J Endocrinol* 2010; 162:747-754. See [Evidence Table](#)

The use of SHBG does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medical necessity review no longer required:

CPT® or HCPC Codes	Description
84270	Sex hormone binding globulin (SHBG)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

**To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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Date Created	Date Reviewed	Date Last Revised
02/14/2011	04/05/2011 ^{MDCRPC} , 02/07/2012 ^{MDCRPC} , 12/04/2012 ^{MDCRPC} , 10/01/2013 ^{MPC} , 08/05/2014 ^{MPC} , 06/02/2015 ^{MPC} , 04/05/2016 ^{MPC} , 02/07/2017 ^{MPC} , 11/07/2017 ^{MPC} , 10/02/2018 ^{MPC} , 10/01/2019 ^{MPC} , 10/06/2020 ^{MPC} , 10/05/2021 ^{MPC} , 10/04/2022 ^{MPC} , 10/03/2023 ^{MPC}	10/21/2020

^{MDCRPC} Medical Director Clinical Review and Policy Committee

^{MPC} Medical Policy Committee

Revision History	Description
04/05/2016	Added exclusion language for symptoms of erectile dysfunction, fatigue, impotence or low libido as the medical literature does not support its use in these circumstances.
10/21/2020	Updated criteria to medical necessity review no longer required to align with current review processes.