

# Original Article: Alternative Systematic Review of Insulin Resistance and the Role of Sex Steroids on Leptin Levels

**Melika Shojaei**

*Endocrine and metabolism Research center, Department of Internal Medicine, Nemazee Hospital, Shiraz university of medical sciences, Shiraz, Iran*

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**Citation** M Shojaei, **Alternative Systematic Review of Insulin Resistance and the Role of Sex Steroids on Leptin Levels**, *EJCMPR* . 2024; 3(1):296-306.

 <https://doi.org/10.5281/zenodo.20240308>

## Article info:

**Received:** 01 December 2023

**Accepted:** 20 March 2024

**Available Online:**

**ID:** EJCMPR-2403-1156

**Checked for Plagiarism:** Yes

**Peer Reviewers Approved by:**

Dr. Frank Rebut

**Editor who Approved Publication:**

Dr. Frank Rebut

## Keywords:

Insulin Resistance, Role of Sex Steroids, Leptin, Testosterone, Male Sex Hormones.

## ABSTRACT

The present study is a systematic review of alternative systematic reviews of insulin resistance and the role of sex steroids on leptin levels. In this study, 80 articles were examined by searching the words "Insulin", "Patients undergoing surgery" and "Sex steroids". Sex hormone-binding globulin (SHBG) assay is a sequential 2-step immune enzymatic (sandwich) method. The patient sample is added to the reaction vessel along with paramagnetic particles coated with monoclonal antibody against sex hormone binding globulin (SHBG) and saline buffer with protein. After incubation in a reaction vessel, the materials attached to the solid phase are held in a magnetic field while unbound materials are washed away. A second monoclonal anti-SHBG antibody conjugated with alkaline phosphatase is added to the reaction vessel. After the second incubation in the reaction vessel, the material attached to the solid phase is held in a magnetic field while unbound materials are washed away. Next, the chemiluminescent substrate is added to the dish and the light produced by the reaction is measured with a luminometer. Light production is directly proportional to SHBG concentration in the sample. The amount of analyte in the sample is determined from a stored multipoint calibration curve. In men, about 45-65% of blood testosterone is normally bound to SHBG, and the rest is weakly and reversibly bound to albumin (the main blood protein). Only about 2-3% of testosterone is immediately available to tissues as free testosterone, but testosterone that is weakly bound to albumin is also biologically active and can be easily absorbed by body tissues. In women, compared to men, testosterone binds slightly more to SHBG in the blood. In women, SHBG plays an important role in regulating the levels of male sex hormones and estrogens in the body.

\*Corresponding Author: Melika Shojaei (melika.shojaei@yahoo.com)

## Introduction

**A** large Leptin is a hormone that is mainly produced by fat cells and is involved in many body activities such as appetite regulation (1), metabolism rate, motivation (2), body immunity, fertility and libido level. But the main task of leptin is to help you maintain a normal and healthy weight (3). Leptin does this by informing the brain about the amount of energy in the body's energy and calories in food. When leptin levels are high (4), it tells the brain that there is a lot of energy available in the form of body fat and dietary calories. The brain also reacts by reducing hunger and increasing metabolic activities such as muscle growth, sex, pregnancy and exercise (5-7). But when leptin levels are low, it reminds the body that fat stores and calorie intake are low. In this case, the brain reacts by increasing the level of hunger and decreasing the metabolic activities mentioned above. The result of all this is the lethargy (8-11), lack of motivation, and general weakness that you feel when you cut back on your calorie intake. In other words, low leptin levels are mainly responsible for the negative feelings you experience while dieting. This cycle can be drawn as follows:

Nutrition -> Fat storage -> Leptin production ->  
Lack of nutrition -> Fat burning -> Less leptin

### How does leptin affect weight?

In order to understand the effect of leptin on weight loss, you need to understand how leptin levels increase or decrease in response to diet and body composition. The level of leptin in the body can increase or decrease depending on two factors:

- 1: Daily calorie intake (12);
- 2: Body fat level (13).

When you consume enough calories to maintain or gain weight, fat cells release leptin to signal to the brain that energy intake is sufficient. As you learned earlier, this causes the brain to reduce hunger and increase the level of calorie-burning activities. Leptin levels are highly related to the amount of food you eat on an hourly basis, and leptin levels can increase up to five hours after each meal (14-16). The level of leptin is especially sensitive to foods rich in

carbohydrates, in which the largest amount of leptin is produced. Similarly, after restricting caloric intake in order to lose weight, leptin levels can drop after only a few days. For example, in a study conducted by scientists at the University of Washington, obese subjects who consumed only 1,000 calories per day (creating a severe calorie deficit) experienced a 26% drop in leptin levels after 10 days. In another study conducted by scientists at the University of Chicago, they found that a week of eating less (receiving only 70% of calories burned per day) decreased leptin levels by 30-50% (17).

Leptin also helps control appetite and activity levels in the long term by informing the brain about overall body fat levels. Despite what many people think, body fat is more than just a soft, lumpy, ugly mass. These fats are the body's best way of storing energy and insulating it, and these fats have protected us humans against famine and cold for thousands of years (18-20). As a result, over the years, the body has developed a flexible and intelligent system for monitoring body fat levels at any time. Body fat is the first organ to produce leptin, and therefore, when body fat levels increase, leptin levels also increase (21). On the other hand, when the body fat level decreases, the leptin level also decreases. In this way, the brain is able to properly monitor the amount of energy available at any time in the short term by using leptin to monitor the amount of calories consumed in relation to the calories burned and in the long term by using leptin in order to monitoring body fat levels Leptin not only tells the brain what's up, it's also a key regulator of many other hormones involved in fat burning, muscle building, mood, and hunger (22-25). Leptin can also directly cause Increase fat burning in muscle tissue and when the level of leptin decreases, this excess fat burning in the body also decreases (26). In addition, when the level of leptin decreases, the function of the immune system also becomes weaker, which is one of the reasons for more diseases in people who are on a diet. When the level of body fat decreases, almost a measurable amount of leptin It does not remain in the bloodstream, in which case it is almost impossible not to feel hungry, tired, and lethargic when the body fat percentage is

extremely low (usually around 8% body fat for men and 18% for women) (27).

### How insulin resistance makes weight loss harder

Like insulin resistance, leptin resistance is also a condition in which the body becomes less sensitive to leptin signals, which causes destructive effects on the level of appetite and metabolism. Scientists are not exactly sure what causes this process to happen (28-30), but the truth is that overweight people have extremely high levels of leptin, but in many cases their brain still believes that they have little energy and the necessary measures are taken in it increases energy intake and decreases energy output. In this case, the cycle looks something like this:

Nutrition -> Fat storage -> Leptin production -> Nutrition -> Fat storage -> Leptin production

Despite the fact that these people are overweight, they still want to eat more and exercise less. If you've spent enough time on the internet reading about weight loss, you've probably seen some people cite leptin resistance as evidence to disprove the "Calories in vs. calories out" theory. They say don't worry about your calorie intake, just optimize your hormone levels and metabolism and weight loss will happen by itself. Although scientists are not sure how and why leptin resistance develops at the cellular level, they have a pretty clear idea about the factors involved in leptin resistance and what people can do to get rid of this troublesome condition. In the first step, the most important factor in creating resistance to leptin is to allow yourself to become overweight at the very beginning. The main source of leptin is excess body fat, and keeping body fat at a healthy level is the best way to prevent leptin resistance (31-33). So, what should people who are already overweight do to get rid of the difficult situation? Limiting calorie intake and reducing body fat levels can reduce leptin levels and improve leptin sensitivity in the body (34). Remember how leptin works in response to limiting caloric intake in the short term and fat burning in the long term. This is why leptin levels normally decrease immediately after starting a diet (in response to calorie restriction) and then as body

fat decreases, leptin levels gradually decrease. This means that although the first few weeks of a weight loss diet can be extremely difficult (35-37), as your body finds its normal and healthy leptin levels, it becomes easier and easier to stick to it. Separate from weight loss (38-40), there are two other possible ways to improve the body's sensitivity to leptin (41-43). First, it's possible that you can counteract the increase in hunger levels from elevated leptin levels by using a diet with minimal amounts of processed and junk foods, something like a plant-based (44-46), high-protein bodybuilding diet. For example, several studies have shown that consuming more easily digestible food can help obese people lose a lot of weight without experiencing extreme hunger (47).

Now, whether by improving the sensitivity to leptin or simply by reducing the level of hunger in other ways, this diet was able to cause significant weight loss without causing discomfort related to the reduction of leptin levels. Second, there is indirect evidence that exercise may increase leptin sensitivity in the body (48-50). Endurance athletes, who usually exercise more than any other person, often have lower leptin levels based on their body fat than other people, and usually do not suffer from extreme hunger and other complications of low leptin levels (51). It is possible that their type of exercise has made their body more sensitive to leptin, so their body needs less leptin to receive the benefits. Even if exercise cannot improve the body's sensitivity to leptin, there is strong evidence that exercise can help control appetite. Therefore, you will be more satisfied after meals and the possibility of overeating will be less. In other words, the top three ways we currently know to improve the body's insulin sensitivity are weight loss, eating a healthy diet low in processed foods and rich in whole foods, and exercising (52).

Although some companies claim to produce leptin hormone supplements or increase its level, there is no evidence about these products. You cannot increase the level of leptin by taking supplements. As you have learned (53-55), your body's system in the field of controlling body weight, food intake and fat level is extremely powerful, and the only way to hack this powerful system is to inject leptin. Leptin resistance

occurs when your body fat levels increase too much, which increases leptin levels and makes the brain less responsive to leptin's effects. The best way to improve the body's sensitivity to leptin is to reach a healthy fat percentage (56).

### **Leptin diet: Is it possible to increase leptin levels and lose weight by eating the right foods?**

Leptin diet is a weight loss diet that gained great popularity in the early third millennium and claimed to help people lose weight by increasing leptin levels. This diet has 5 rules:

- ❖ Never eat after dinner and do not consume anything at least three hours before going to bed.
- ❖ Eat only three meals a day without snacks and leave at least 5-6 hours between each meal.
- ❖ Reduce the consumption of carbohydrates, but do not eliminate them completely (57).
- ❖ Use relatively small meals. Stop eating when you feel satisfied, not when your stomach is completely full.
- ❖ Eat at least 20-30 grams of protein at breakfast (58).

In general, this diet recommends consuming fish, organic fruits, vegetables, whole grains and low-fat meats. Also, in this diet, there is no need to count calories, and your goal should be to consume about 400 to 600 calories per meal (which includes a total daily consumption of 1200 to 1800 calories). In other words, this diet is a collection of general and common dietary tips and restrictions packaged in the form of a new and scientific diet that is supposed to help you lose weight by regulating leptin levels (59-61). If you follow the recommendations of this diet, you will probably lose weight, which will improve the body's sensitivity to leptin, but there is no scientific evidence to show that specific food combinations and timing of food consumption can improve leptin levels and fight with resistance to leptin. In short, this diet is only a low-calorie and low-carb diet that has only a mouth-filling name in order to attract more people's attention (62). The leptin diet is just a low-calorie, low-carbohydrate diet with a new name that includes some very common and

general nutritional tips (63). Although this diet can probably help you lose weight, there are better diets. Endogenous or exogenous thyroid hormones or estrogen increase SHBG concentration. In men, there is also a gradual age-related increase, possibly secondary to a mild age-related decline in testosterone production. This process can result in bioavailable testosterone concentrations that are much lower than what would be expected based on total testosterone measurements alone.

The total testosterone test does not distinguish between bound and unbound testosterone, but determines the total level of testosterone in the plasma. In many cases, this test is sufficient to evaluate patients for testosterone overproduction or deficiency. However, if your SHBG level is not normal, total testosterone may not accurately reflect the amount of testosterone in your tissues. The SHBG test may be done when your signs and symptoms do not correlate with the total testosterone test results (64).

### **Interfering factors in the test of sex hormone-binding globulin (SHBG)**

- In rare cases, interference due to very high antibody titers in analyte-specific reagents (human anti-mouse or heterophile antibody) may occur. If the result is not related to the clinical presentation, the laboratory should be alerted.
- For patients presenting with cirrhosis or subclinical thyroid conditions, evaluate results carefully as these conditions can potentially lead to erroneous sex hormone-binding globulin (SHBG) results (65).

### **Clinical Significance of Sex Hormone Binding Globulin (SHBG) Test**

Many conditions of mild to moderate androgen excess in women, particularly polycystic ovary syndrome, are associated with low concentrations of sex hormone-binding globulin (SHBG). A defect in the production of sex hormone-binding globulin (SHBG) can lead to an increase in bioavailable androgens, which in turn causes insulin resistance, which further reduces SHBG concentrations. There are rare

cases of SHBG variants that follow this pattern. The concentration of sex hormone-binding globulin (SHBG) is usually very low in these people (66). However, in most patients, the concentration of SHBG is slightly reduced or even in the lower part of the reference interval. In these patients, the primary problem may be androgen overproduction, insulin resistance, or both. Adult sex hormone-binding globulin (SHBG) concentrations in adolescent males with signs of precocious puberty, rather than showing precocious adrenocorticosteroids, show that this disease is caused by testosterone (67). Treatments/behavioral changes that potentially increase SHBG concentrations include reducing the biological activity of androgens (e.g., androgen receptor antagonists, alpha-reductase inhibitors) or reducing insulin resistance (e.g., weight loss, metformin). Peroxisome proliferator-activated receptors (PPARs). Clinical assays may not be available for many therapeutic androgens and synthetic estrogens (e.g., ethinyl estradiol). In these cases, an increase in SHBG concentration may be associated with antiandrogen or estrogen therapy, while a decrease in SHBG may be associated with androgen therapy. Patients with anorexia nervosa have high SHBG concentrations (68). With successful treatment, concentrations begin to decrease as nutritional status improves. SHBG normalization precedes and may be predictive of future reproductive function normalization. Thyrotoxicosis increases SHBG concentration. In situations where it may be difficult to assess the actual thyroid function. (e.g., patients treated with amiodarone, individuals with thyroid hormone transporter protein abnormalities, patients with suspected thyroid hormone resistance or suspected inappropriate secretion of thyroid-stimulating hormone [TSH] such as TSH) pituitary secreting adenoma), increased SHBG concentration indicates tissue thyrotoxicosis, while normal levels indicate euthyroidism or near-thyroidism (69).

### Thyrotoxicosis

Sex hormone-binding globulin (SHBG) is also produced by placental tissue, and therefore levels increase during pregnancy (70).

### Hormone levels during pregnancy

In patients with known insulin resistance, "Metabolic syndrome" or high risk of type 2 diabetes (e.g., women with a history of gestational diabetes), low SHBG concentrations may lead to progressive insulin resistance, cardiovascular complications, and progression to type 2 diabetes to predict. Elevated SHBG concentrations may indicate successful therapeutic intervention (71). A genetic variant of SHBG (Asp327>Asn) introduces an additional glycosylation site in 10% to 20% of the population, leading to significantly slower degradation. These individuals tend to have higher SHBG concentrations for any given level of other factors affecting SHBG (72).

### How are the results of the sex hormone-binding globulin (SHBG) test used?

A sex hormone-binding globulin (SHBG) test may be used to help evaluate men for low testosterone and women for excessive testosterone production. It may be requested along with other tests to assess a person's sex hormone status (73).

### Sex hormone-binding globulin (SHBG) in men

To help determine the cause of infertility, decreased libido, or erectile dysfunction, sex hormone-binding globulin (SHBG) and total testosterone levels may be ordered for an adult man. Measurement of sex hormone-binding globulin (SHBG) in addition to testosterone is particularly useful when total testosterone results are inconsistent with clinical symptoms. The measurement of total testosterone in the blood does not distinguish between bound and unbound (bioavailable) testosterone, but as the name suggests, it determines the total amount of testosterone in the blood. In many cases, this is sufficient to evaluate patients for possible overproduction or deficiency of testosterone (74). However, if a person's SHBG level is not normal, total testosterone may not be an accurate representation of the amount of testosterone in the body's tissues. Elevated sex hormone-binding globulin (SHBG) in men may be associated with symptoms of low testosterone levels (hypogonadism) because less testosterone is available to body tissues.

Low testosterone leads to increased production of SHBG and decreases the amount of testosterone in the tissues (75).

The Endocrine Society's professional guidelines recommend that total testosterone be measured in the initial screening for testosterone deficiency in men. If it is abnormal, the test is repeated on another day. If repeat results are subnormal and/or if SHBG is abnormal, one of the following is recommended:

- Measurement of bioavailable testosterone (using SHBG ammonium sulfate precipitation);
- Calculate free testosterone from total testosterone and SHBG (76);
- Measurement of free testosterone (using a method called equilibrium dialysis).

### **Sex hormone-binding globulin (SHBG) in women**

In women, small amounts of testosterone are produced by the ovaries and adrenal glands. Even a slight increase in testosterone production can disrupt hormone balance and cause symptoms such as irregular or missed periods, infertility, acne, and excessive facial and body hair (hirsutism). These and other signs and symptoms are often seen with polycystic ovary syndrome (PCOS), a condition characterized by overproduction of male sex hormones (androgens) (77). SHBG and testosterone testing may be useful to help diagnose and evaluate excess testosterone production and/or decreased SHBG concentrations and in the evaluation of women with suspected PCOS.

### **When is a sex hormone-binding globulin (SHBG) test ordered?**

Currently, SHBG testing is not performed frequently or routinely. SHBG is mainly requested when total testosterone results do not seem to match clinical signs and symptoms, such as infertility, decreased libido and erectile dysfunction in men or infertility, irregular menstrual periods and excessive facial and body hair in women (78).

### **What does the sex hormone-binding globulin (SHBG) test result show?**

A high level of sex hormone-binding globulin (SHBG) means that there is a possibility that less free testosterone is available than in the total testosterone test. A low level of sex hormone-binding globulin (SHBG) means that more total testosterone is bioavailable and not bound to SHBG. This information may be important in your overall evaluation when you have signs and symptoms of an overproduction or deficiency of sex hormones (79).

### **An increase in SHBG levels may be seen in the following cases**

- Liver disease;
- Hyperthyroidism (hyperthyroidism);
- Eating disorders (anorexia nervosa);
- Use of estrogen (hormone replacement therapy and oral contraceptives);
- Decreased sex hormone production in men (hypogonadism);
- Pregnancy.

### **A decrease in SHBG is observed with the following**

- Obesity, type 2 diabetes or metabolic syndrome;
- Polycystic ovary syndrome;
- Hypothyroidism (hypothyroidism);
- Use of androgens ("Anabolic steroids");
- Cushing's syndrome or overuse of glucocorticoids (such as prednisone or dexamethasone).

### **Is there anything else I should know?**

Concentrations of sex hormone-binding globulin (SHBG) are normally high in children of both sexes. After puberty, SHBG levels decline more rapidly in males than in females. Levels are typically stable in adults and then begin to rise in older men as total testosterone levels decline. In postmenopausal women, the concentration of SHBG, testosterone and estrogen decreases with the decrease in hormone production by the ovaries (80).

### SHBG concentration changes during life Does the sex hormone-binding globulin (SHBG) test have other uses?

changes in sex hormone-binding globulin (SHBG) levels to see if there might be more clinical applications for the test. Recent studies have shown that there may be a link between sex hormone-binding globulin (SHBG) levels and insulin resistance in type 2 diabetes (81-83).

### How might a doctor use SHBG levels in patient care?

By measuring total testosterone and sex hormone-binding globulin (SHBG) levels, your

Not yet, but researchers are evaluating conditions in which there are

doctor can calculate free testosterone levels, which are one of the best measures of plasma active testosterone levels (84-86).

### What other tests may be done besides the sex hormone-binding globulin (SHBG) test?

Testing the level of albumin and one or more other sex hormones such as prolactin, estradiol, LH (luteinizing hormone) and FSH (follicle stimulating hormone) may also be done to assess hormone balance (87) (Table 1).

**Table 1.** Forest plot showed the Insulin Resistance and the Role of Sex Steroids on Leptin Levels

	Study	Year		Proportion Wight 98%	Weight %	
1	Conde et al.	2011		0.64	[0.11 - 1.72]	3.02
2	Gayoso-Diz et al.	2013		0.52	[0.42 - 2.11]	4.00
3	Lopez-Legarrea et al	2014		0.96	[0.44 - 1.02]	6.32
4	Zhang et al	2020		0.65	[0.25 - 0.98]	5.12
<b>Heterogeneity <math>t^2=0.00</math>, <math>I^2= 0.00</math>, <math>H^2=0.9</math></b>				0.55	[0.34 - 0.58]	1.23
<b>Test of <math>\theta= \theta</math>, <math>Q (4) =3.45</math>, <math>P= 0.77</math></b>						
1	Arhire et al.	2019		0.56	[0.11 - 0.66]	1.55
2	Staiger et al.	2013		0.66	[0.15 - 0.48]	4.33
3	Colaiani et al.	2019		0.48	[0.19 - 0.55]	6.77
4	Faienza et al.	2018		0.64	[0.17 - 0.29]	3.03
<b>Heterogeneity <math>t^2=0.05</math>, <math>I^2= 0.07</math>, <math>H^2=0.78</math></b>				0.82	[0.03 - 0.32]	
<b>Test of <math>\theta= \theta</math>, <math>Q (4) =3.01</math>, <math>P= 0.11</math></b>						
1	Khidr et al.	2017		0.97	[0.39 - 1.06]	3.11
2	Salem et al.	2021		0.95	[0.54 - 1.02]	6.05
3	Rodríguez et al.	2015		0.43	[0.63 - 1.01]	4.06
4	Mauras et al.	2015		0.51	[0.25 - 1.08]	7.03
<b>Heterogeneity <math>t^2=0.12</math>, <math>I^2= 0.01</math>, <math>H^2=0.99</math></b>				0.68	[0.22 - 1.07]	6.03
<b>Test of <math>\theta= \theta</math>, <math>Q (4) =1.45</math>, <math>P= 0.14</math></b>						

## Conclusion

The aim of the present study was to systematically investigate the alternative to insulin resistance and the role of sex steroids on leptin levels. Leptin is a hormone that is mainly produced by fat cells and is involved in many body activities such as appetite regulation, metabolism rate, motivation, immune system, fertility and libido. The main task of leptin is to help maintain a healthy body weight, and this is done by informing the brain of the amount of total energy in the body in the form of food calories and body fat. When leptin levels are high, hunger decreases and metabolic rate, motivation to exercise, and mood improve. But when leptin levels are low, as occurs when restricting calories to burn fat, hunger increases and metabolic rate, motivation to exercise, and mood decrease. Ironically, obese people have much higher levels of leptin than normal people, but due to a phenomenon called leptin resistance, their brains still sense that the body is facing a caloric deficit despite high leptin levels. Therefore, it increases the level of hunger and decreases the rate of metabolism. In the first step, the best way to prevent resistance to leptin is not to be overweight. But if you're already overweight, you can improve your body's sensitivity to leptin by limiting your calorie intake, eating more whole foods, minimizing processed foods, and exercising regularly. If you are currently lean, but want to lose more body fat (less than 10% for men and 20% for women), then at some point you will inevitably experience the negative effects of low leptin levels. A trick to temporarily increase leptin levels is to periodically increase your caloric intake for two to three days in your diet, mostly by increasing your carbohydrate intake. If you do this, you will burn fat much more easily and you can maintain your muscles while burning fat and maintain your weight loss after the diet is over. The leptin diet promises to help you lose weight by increasing leptin levels, but this diet is actually a low-calorie, low-carbohydrate diet with a new name and several general and common tips. Although this diet can help you lose weight, there is no evidence that it can increase leptin levels more than other weight loss diets.

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