

Impact of diet and adiposity on circulating levels of sex hormone-binding globulin and androgens

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This review summarizes studies on the effect of various diets on circulating androgen levels and sex hormone-binding globulin (SHBG). Reduced caloric intake leading to significant weight loss increases SHBG levels regardless of diet composition, particularly in women. Cross-sectional studies show that dietary composition is generally not associated with SHBG levels independent of obesity level. No clear conclusion can be reached regarding the effect of various eating habits or dietary composition on circulating androgens. The evidence indicates that dietary effects on circulating SHBG, and possibly androgens, can be expected if body weight or fatness and/or insulin homeostasis are modulated.

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INTRODUCTION

Sex hormones have many important biological roles in growth, sexual maturation, and reproduction. They also play a role in hormone-dependent cancers such as breast and prostate cancer.¹ Circulating sex hormone levels are also associated with metabolic parameters such as obesity and body fat distribution.² In men, low circulating androgens including testosterone, dehydroepiandrosterone (DHEA), androstenedione (4-dione), androstenediol, and dihydrotestosterone (DHT) have been associated with obesity and increased accumulation of fat within the abdominal cavity, termed visceral fat.^{2,3} In women, high levels of free and total androgens have been reported in women with polycystic ovary syndrome (PCOS), who are frequently characterized by abdominal obesity.⁴ However, the association between circulating androgens and obesity in women without PCOS remains equivocal.⁵

Sex hormone-binding globulin (SHBG) is a circulating sex steroid transporter secreted by the liver.⁶ Approximately 65% of serum testosterone is bound to SHBG.⁷ Another portion is bound to albumin (~33%). The free

moiety of testosterone (Free-T, FT) has been considered as the active fraction and represents approximately 2% of total testosterone.⁷ Consequently, bioavailable testosterone or free testosterone levels have been inversely related to the levels of SHBG.⁸

Several studies have now suggested an impact of diet and metabolic status on circulating levels of androgens and SHBG.^{9,10} Such an impact could be mediated by specific effects of given nutrients or by other metabolic pathways such as diet-induced changes in the level of obesity or insulin resistance.¹¹ To date, however, the literature remains inconclusive as to whether diet plays a direct role in the regulation of androgens and SHBG or whether its effects are mediated by dietary-induced metabolic fluctuations.

This article summarizes studies that have examined the impact of diet on circulating androgens and SHBG in men and women to clarify whether dietary effects on androgenicity are mediated by their impact on adiposity or insulinemia. We tested the hypothesis that changes in body fat mass will have the most important impact on circulating concentrations of androgens and SHBG, independent of diet composition *per se*.

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METHODOLOGICAL CONSIDERATIONS

Studies that have examined the effects of different diets on circulating androgen levels and SHBG were considered. Searches of the PubMed database were performed using the following key words: SHBG, androgen, diet, nutrition, nutritional intervention, and sex hormones. Relevant references in the literature obtained were further reviewed to identify additional studies on this topic. All types of dietary patterns were included, such as diets that were low in fat, low in carbohydrates, high in fiber, high in monounsaturated fat, etc. All research designs were examined and separated into two broad categories: intervention studies and cross-sectional studies. For these two types of study designs, we considered whether diet induced a significant weight loss or whether a given diet was associated with body composition or body weight differences respectively. Insulinemia was also considered when data was available. Finally, men and women of all ages and metabolic conditions were included in the analysis, but were examined separately where relevant.

INTERVENTION STUDIES

Sex hormone-binding globulin

Several studies investigated the effect of various dietary interventions on circulating SHBG. Overall, according to most reports, a reduction in total energy intake leading to significant weight loss seems to be linked to an increase in SHBG levels in women (summarized in Table 1). For example, Berrino et al.¹² examined the impact of an *ad libitum* Mediterranean vegetarian diet on testosterone and SHBG levels in postmenopausal women by studying two groups of 52 women. The intervention group received dietary counselling, common meals, and cooking classes to maintain the prescribed diet for 4.5 months. Subjects from the control group did not receive any information about diet and were advised to increase their fruit and vegetable consumption. At the end of the trial, women of the intervention group showed a significant weight loss and a reduced BMI compared with the control group. This reduction in BMI was associated with a concomitant increase in SHBG levels. Interestingly, when adjusting for weight loss, no significant change was observed in SHBG levels between the two groups. Kaaks et al.,¹³ studied the same cohort to measure the impact of the *ad libitum* Mediterranean diet on insulin sensitivity. Women in the intervention group ($n = 50$) who had an increase in SHBG level also had a significant decrease in insulin area and in fasting glucose compared to women in the control group ($n = 49$). A decrease was also observed in fasting insulin, but it did not reach significance. In another study by Tymchuk et al.¹⁰ similar results were

obtained: 22 postmenopausal women (11 on hormone replacement therapy [HRT] and 11 not on HRT), followed a low-fat (10% fat calories) and high-fiber (35–40 g/1000 kcal each day) diet with exercise for a period of 3 weeks. After the intervention, BMI was significantly reduced and SHBG levels were significantly higher in the two groups, independent of HRT use. These changes were associated with a significant decrease in serum insulin.

In postmenopausal women with type 2 diabetes, Walker et al.¹⁴ examined the effect of a 12-week high-carbohydrate diet versus a 12-week high-monounsaturated-fat diet using a crossover design with a 4-week washout. Body weight was not affected by the diets but fat mass was significantly reduced by both diets; this reduction was most important with the high-carbohydrate diet. A slight increase was observed in SHBG levels but it remained non-significant. Insulin measures were not included in that analysis. Blouin et al.⁶ also observed an increase in SHBG levels after a 6-week National Cholesterol Education Program (NCEP) Step 1 diet (<30% of total energy from fat, <10% of energy from saturated fat) leading to significant weight loss. The SHBG increase was independent of insulinemia.

Conversely, in an 8-week crossover trial in postmenopausal women, no change in body weight was observed, but SHBG levels were still increased when women consumed an isocaloric lean-white-fish diet compared to a regular or isocaloric diet essentially composed of beef, pork, egg, and milk.¹⁵ Thus, independent of weight loss, the lean-white-fish diet had an impact on SHBG levels which was also linked to improvements in lipid profile.¹⁵ Fish protein has been shown to have a positive effect on glucose and insulin homeostasis.¹⁶ In that particular case, we can suppose that the increase in SHBG levels observed could be associated with a possible improvement of insulin sensitivity caused by the consumption of fish protein. However, this hypothesis cannot be confirmed as no insulin measures were performed. Changes in SHBG levels independent of weight loss were also observed in a different cohort composed of premenopausal women.¹⁷ A 4-week baseline high-fat and low-fiber diet was followed by an isocaloric low-fat and high-fiber diet for 8–10 weeks and no change in body weight was observed, but surprisingly, the low-fat and high-fiber diet produced a decrease in SHBG levels. These results contradict some cross-sectional studies that found higher SHBG levels in long-term vegetarians (see below).^{7,18} The authors suggest there is an initial decline in SHBG in the first few months after increasing fiber intake, a trend that would be reversed after an extended time on a high-fiber diet.¹⁷ Insulin measures were not included in the analysis.

Bennett et al.¹⁹ also obtained divergent results in a cohort of premenopausal women who followed their usual diet or a vegetarian diet or a fish-diet at least 3 times

Table 1 Changes in SHBG levels, adiposity measures and insulinemia in women undergoing dietary intervention studies.

Study	Population	Design	Intervention	Results
Berrino et al., (2001) ^{12*}	104 postmenopausal women (50–65 years)	Randomized controlled trial	Dietary counselling and cooking classes to maintain 4.5-month <i>ad libitum</i> Mediterranean vegetarian diet (n = 52) or usual standard diet (control diet) (n = 52)	<ul style="list-style-type: none"> ↓ Body weight ($p \leq 0.0001$), ↓ BMI ($p \leq 0.0001$), and ↑ SHBG ($p \leq 0.0001$) in the intervention group No insulin measurements
Kaaks et al., (2003) ^{13*}	99 postmenopausal women (50–65 years)	Randomized controlled trial	Dietary counselling and cooking classes to maintain 4.5-month <i>ad libitum</i> Mediterranean vegetarian diet (n = 50) or usual standard diet (control diet) (n = 49)	<ul style="list-style-type: none"> ↓ Body weight ($p \leq 0.0001$) ↓ BMI ($p \leq 0.0001$) ↑ SHBG ($p \leq 0.0001$) ↓ Insulin area ($p = 0.04$) ↓ Fasting glucose ($p = 0.03$) in the intervention group
Tymchuck et al., (2000) ^{10*}	22 postmenopausal women (64.1 ± 1.7 years)	Diet change	3-week low-fat (10% fat calories) high-fiber diet (35–40 g/1000 kcal/day) in all women (11 women on HRT and 11 women not on HRT)	<ul style="list-style-type: none"> ↓ Body weight ($p \leq 0.01$) ↓ BMI ($p \leq 0.01$) ↓ Serum insulin ($p \leq 0.01$) ↑ SHBG ($p \leq 0.01$) in all women
Walker et al., (1999) ^{14*}	34 women with type 2 diabetes (58.0 ± 7.0 years)	Randomized crossover trial	12-week high-CHO diet (60% CHO calories) and 12-week high-MUFA diet (20% MUFA fat calories) in random order (4-week washout) in all women	<ul style="list-style-type: none"> ↓ Total body fat mass ($p = 0.02$) No significant change in body weight No significant change in SHBG No insulin measurements
Blouin et al., (2007) ^{6*}	35 premenopausal overweight women (38.6 ± 7.4 years)	Randomized controlled trial	6-week NCEP Step 1 diet (<30% of total energy from fat, <10% of energy from saturated fat) with (intervention diet) (n = 18) or without an oat bran supplementation (control diet) (n = 17)	<ul style="list-style-type: none"> ↓ Body weight ($p = 0.005$), ↓ BMI ($p = 0.005$), and ↑ SHBG ($p = 0.0005$) No significant change in fasting insulin in both groups
Jacques et al., (1992) ¹⁵	15 postmenopausal women (62.5 ± 0.3 years)	Randomized crossover trial	4-week lean-white-fish (LWF) diet and 4-week beef, pork, egg, and milk (BPEM) diet in random order (no washout)	<ul style="list-style-type: none"> No significant change in body weight ↑ SHBG ($p \leq 0.01$) with LWF diet No insulin measurements
Goldin et al., (1994) ¹⁷	48 premenopausal women (27.1 ± 4.3 years)	Diet change	4-week high-fat (40% fat calories) low-fiber (12 g/day) diet (control diet) followed by 8–10-week isocaloric low-fat (20–25% fat calories) high-fiber (40 g/day) diet in all women	<ul style="list-style-type: none"> No significant change in body weight ↓ SHBG ($p \leq 0.001$) with low-fat high-fiber diet No insulin measurements
Bennett et al., (1990) ^{19*}	39 premenopausal women (21–52 years)	Randomized controlled trial	3-month vegetarian diet (n = 13) or 3-month fish diet (n = 13) or 3-month usual standard diet (control diet) (n = 13)	<ul style="list-style-type: none"> No significant change in body weight No significant change in SHBG for all diets No insulin measurements

Woods et al., (1996) ^{20*}	21 premenopausal women (26.7 ± 5.1 years)	Diet change	3-week high-fat (40% fat calories) low-fiber (12 g/day) diet (control diet) followed by 7–10-week isocaloric low-fat (20% fat calories) high-fiber (40 g/day) diet in all women	No significant change in body weight No significant change in SHBG with low-fat high-fiber diet No insulin measurements
Gann et al., (2003) ^{21*}	213 premenopausal women (20–40 years)	Randomized controlled trial	18 group classes and 2 individual meetings to maintain 1-year isocaloric low-fat (20% fat calories) high-fiber (25 g/day) diet (with at least 8 servings of fruits/day) (n = 106) or usual standard diet (control diet) (n = 106)	No significant change in body weight No significant change in BMI No significant change in SHBG in the intervention group No insulin measurements
Rock et al., (2004) ^{22*}	291 women with history of breast cancer (57.0 ± 8.0 years)	Randomized controlled trial	1-year low-fat (21% fat calories) high-fiber (29 g/day) diet (n = 153) or usual standard diet (control diet) (n = 138)	No significant change in body weight No significant change in SHBG in the intervention group No insulin measurements
Moran et al., (2003) ^{23*}	28 overweight women with PCOS (33.0 ± 0.8 years)	Randomized controlled trial	12-week energy-restricted diet low in protein (15% protein calories) (n = 14) or high in protein (30% protein calories) (n = 14) followed by a 4-week period of weight maintenance	↓ Total body fat mass (p ≤ 0.001) ↓ Fasting insulin (p ≤ 0.001) ↓ HOMA index (p ≤ 0.001) ↑ SHBG (p = 0.03) in both groups
Kiddy et al., (1989) ^{24*}	5 overweight women with PCOS and 6 normal-weight women (age NR)	Diet change	2–4-week VLCD (330 kcal) in all women	↓ Body weight (p = NR) and ↑ SHBG (p ≤ 0.02) after 2 weeks in both groups ↓ Fasting insulin (p ≤ 0.05) in women with PCOS after 2 and 4 weeks
Franks et al., (1991) ^{11*}	263 women with PCOS (age NR)	Diet change	2-week VLCD (350 kcal) in all women and 6–7-month LCD (1000 kcal) in a subgroup of 24 women	↓ Body weight (p = NR) ↓ Fasting insulin (p = NR), and ↑ SHBG (p = NR) for both protocols
Crave et al., (1995) ^{25*}	24 obese hirsute women (age NR)	Randomized controlled trial	4-month LCD (1500 kcal) with or without metformin administration	↓ BMI (p ≤ 0.00001), ↓ fasting insulin (p ≤ 0.01), and ↑ SHBG (p ≤ 0.001) with low calorie diet without metformin administration

Abbreviations: NR, not reported in the original article; HRT, hormone replacement therapy; CHO, carbohydrate; MUFA, monounsaturated fatty acid; NCEP, National Cholesterol Education Program; LCD, low-calorie diet; PCOS, polycystic ovary syndrome; VLCD, very-low-calorie diet.

* These studies observed an inverse association between SHBG levels and adiposity measures (87% of all studies listed).

per week. After 3 months, body weight was maintained and no change in circulating levels of SHBG was observed. Similarly, a study by Woods et al.²⁰ including 21 healthy African-Asian premenopausal women who followed an isocaloric, low-fat (20%), high-fiber diet for 7–10 weeks found no significant change in SHBG levels, and this was associated with maintained body weight. Gann et al.²¹ also found that an isocaloric low-fat (20%) and high-fiber diet did not induce any changes in either body weight or SHBG levels. Another interesting study including 291 women, this time with a history of breast cancer, examined the impact of a high-fiber, low-fat diet and did not observe any change in body weight and SHBG levels.²² In these studies, diet composition seemed to have no impact on SHBG levels.

In women with PCOS, the situation is confounded by a marked hyperandrogenic status. However, studies that have been conducted have generated similar results: weight loss induced by a caloric-restrictive diet is directly linked to an increase in SHBG levels. For example, a randomized control trial including 28 overweight women with PCOS demonstrated that an energy-restricted diet (~1400 kcal) of 12 weeks' duration followed by a 4-week period of weight maintenance increased SHBG levels, irrespective of whether women were on a low- or high-protein diet.²³ In both groups, a significant weight loss and a significant decrease in fat mass was observed and associated with a 20% decrease in fasting insulin and a 9% decrease in HOMA index. Similar results were observed in a study by Kiddy et al.²⁴ in which five obese women with PCOS were compared to six normal-weight, healthy women. After 2–4 weeks of a very-low-calorie diet (330 kcal) weight loss was observed in both groups and was associated with a twofold increase in SHBG levels, which was mirrored by a concomitant decrease in serum insulin. Another study testing the impact of a very-low-calorie diet (350 kcal) for 2 weeks in 263 women with PCOS observed weight loss with a decrease in fasting insulin, leading to a concomitant twofold increase in SHBG levels. Similar results were observed during a long-term (6–7 months) 1000 kcal calorie diet.¹¹ Finally, in 24 hirsute women, a low-calorie diet of 1500 kcal also induced a decrease in BMI and a significant increase in SHBG levels, as well as a significant decrease in serum insulin.²⁵ Androgenic and insulin statuses of these women were both improved at the end of the protocol and some of the subjects demonstrated improved menstrual function and fertility.^{11,23}

In summary, in both pre- and postmenopausal women, the majority of studies showed that changes in body weight are an important predictor of increased SHBG levels in response to dietary intervention. When body weight is maintained, the situation is less clear, but most studies observed no change in circulating SHBG

levels, which is also consistent with weight loss being a determinant factor. Insulin measures were not available in all studies, but an improvement in insulinemia seems to be an important predictor of improved SHBG levels, especially in women with PCOS. Taken together, the available data show that diets leading to weight loss in women are associated with an increase in SHBG levels in a majority of studies. This finding appears to be independent of hormonal status, metabolic status, and diet composition *per se*.

Weight loss studies are less abundant in men than in women (summarized in Table 2). One study including 39 healthy, middle-aged men first examined the subjects' usual diet (high-fat and low-fiber) before they switched to an 8-week isocaloric, high-fiber, and low-fat diet. After a small weight loss of 1 kg, a small but significant decrease in SHBG levels was detected at the end of the trial. No information on insulin was provided in that study.²⁶ Conversely, another study including 20 healthy men examined the effect of a 6-week carbohydrate-restricted diet. Even after an average reduction of 3.4 kg of body weight associated with a decrease in circulating concentrations of insulin, no significant change was observed in SHBG levels.²⁷ In a three-phase study, 30 healthy men first consumed their usual diet for 2 weeks, followed by a low-fat diet for 6 weeks and finally returned to their usual diet for another 6 weeks. A trend for a reduced sex hormone-binding capacity of SHBG was observed in association with a small weight loss after the intervention period. No insulin data was provided.²⁸ When obese (BMI > 35 kg/m²) men were examined after a very-low-calorie diet, weight loss was clearly associated with an increase in SHBG levels in two similar studies.^{29,30} One of these studies observed an improvement in insulin sensitivity (QUIKI)²⁹ and the other observed a significant decrease in plasma insulin levels.³⁰ The reverse situation was also studied: 12 pairs of young, sedentary, male monozygotic twins were overfed for a period of 100 days (1000 kcal energy excess/day).³¹ Significant weight gain was associated with a fall in SHBG levels in that study, consistent with the opposite trend observed in the majority of weight loss studies.

In the absence of significant weight loss, only one study observed changes in SHBG levels. This crossover trial compared an isocaloric 10-day high-protein diet (44% protein) versus an isocaloric 10-day high-carbohydrate diet (70% carbohydrate). SHBG levels were significantly higher with the high-carbohydrate diet compared to the high-protein diet in the absence of weight loss.³² This change is possibly due to increased fiber intake in the high-carbohydrate diet, or is perhaps associated with an improvement in glucose-insulin homeostasis. However, insulin measures were not included in the analysis.

Table 2 Changes in SHBG levels, adiposity measures, and insulinemia in men undergoing dietary intervention studies.

Study	Population	Design	Intervention	Results
Wang et al., (2005) ²⁶	39 healthy men (54.2 ± 0.5 years)	Diet change	Usual standard diet (baseline diet) followed by 8-week isocaloric low-fat high-fiber diet	↓ Body weight ($p = 0.002$), ↓ BMI ($p = 0.003$), and ↓ SHBG ($p = 0.01$) after the intervention period No insulin measurements
Volek et al., (2002) ²⁷	20 healthy men (36.7 ± 11.6 years)	Randomized controlled trial	6-week CHO-restricted diet (8% CHO) ($n = 12$) or usual standard diet (control diet) (48% carbohydrate) ($n = 8$)	↓ Body weight ($p \leq 0.05$), ↓ total body fat mass ($p \leq 0.05$), ↓ serum insulin ($p \leq 0.01$), and no significant change in SHBG in the intervention group
Hamalainen et al., (1984) ²⁸	30 healthy men (40–49 years)	Diet change	2-week usual standard diet followed by 6-week low-fat diet transferred back to 6-week usual standard diet	↓ Body weight ($p = NR$) and ↓ SHBG ($p \leq 0.07$) after the intervention period No insulin measurements
Niskanen et al., (2004) ^{29*}	58 obese men (46.3 ± 7.5 years)	Diet change	Usual standard diet (baseline diet) followed by 9-week very-low-calorie diet (800 kcal), followed by 12-week weight maintenance	↓ Body weight ($p \leq 0.001$), ↑ insulin sensitivity (QUICKI), and ↑ SHBG ($p \leq 0.001$) after the intervention period
Kaukua et al., (2003) ^{30*}	38 obese men (46.6 ± 9.9 years)	Randomized controlled trial	4-month weight loss program including 10-weeks on a very-low-calorie diet and 17 behavior visits ($n = 19$) or no intervention in the control group ($n = 19$), 8-month follow-up	↓ Body weight ($p \leq 0.001$), ↓ BMI ($p \leq 0.001$), ↓ serum insulin ($p \leq 0.001$), and ↑ SHBG ($p \leq 0.001$) after the intervention and the follow-up period
Pritchard et al., (1998) ^{31*}	12 pairs of male twins (21.0 ± 2.0 years)	Diet change	100 days of overfeeding (1000 kcal energy excess/day) for all pairs of twins	↑ Body fat mass ($p \leq 0.0001$), ↑ BMI ($p \leq 0.0001$), and ↓ SHBG ($p \leq 0.0001$) for all pairs of twins after the intervention No insulin measurements
Anderson et al., (1987) ³²	7 healthy men (22–43 years)	Diet change	10-day high-protein diet (44% proteins calories) followed by 10-day isocaloric high-CHO diet (70% carbohydrate calories) for all men	No significant change in body weight and ↑ SHBG ($p \leq 0.01$) with the high-carbohydrate diet No insulin measurements

* These studies observed an inverse association between SHBG levels and adiposity measures (43% of all studies listed).
Abbreviations: NR, not reported in the original article; CHO, carbohydrate.

In general, even with significant weight loss in men, the increase in SHBG levels was less pronounced than in women. A trend for increased SHBG levels was observed more specifically in obese men, concomitant with a lower body weight and a better insulin profile, in response to the intervention.

Circulating androgens

Available literature on diet and circulating androgens is generally difficult to interpret and equivocal. Various hormones have been examined using various methodologies. Furthermore, the results are far less consistent than for SHBG.

In both men and women, an increase in total testosterone levels was noticed in some studies reporting both weight loss and increased SHBG levels.^{29,30,33} In two other studies in which SHBG was unaltered, no change in testosterone was observed, even with a reduction in body fat mass or weight.^{14,27} Conversely, even when weight loss was significant and increased SHBG levels were reported, some studies observed a decrease in total testosterone levels.^{12,23} Another study observed such reduction, but only in free testosterone levels.²⁴ Two studies reported different results, that is, a decrease in SHBG and a reduction in body weight associated with a reduction in total testosterone, free-T, and 4-dione levels.^{26,28} When weight gain was induced, DHEA-S, total testosterone and DHT were unaltered even with a decrease in SHBG levels.³¹ Thus, according to available dietary intervention results, even when weight reduction is significant, we could not reach any firm conclusion due to several discrepancies among available reports. Differences across these trials possibly include type and length of the diets tested, hormone measurements performed, and sex of the subjects.

In the absence of weight loss, results are also inconclusive in both men and women. In a randomized controlled trial in which 13 healthy South African black men were compared to 21 South African men with prostate cancer after following a Western diet (40% fat), testosterone, 4-dione, and DHEA levels were decreased in both groups.³⁴ Another study that had observed an increase in SHBG levels in seven healthy men showed higher testosterone levels after a high-carbohydrate diet without changes in plasma DHEA and 4-dione.³² In a crossover study in which 43 healthy men consumed a low-fat and high-fiber diet for 10 weeks followed by a high-fat and low-fiber diet for 10 weeks, mean plasma concentrations of total and SHBG-bound testosterone were higher on the high-fat and low-fiber diet,³⁵ a finding that is different from most studies. In women, two studies that did not observe any change in SHBG levels found no change in either testosterone¹⁹ and 4-dione or DHEA levels.²² Of

these two randomized trials, one was conducted in women with breast cancer following a diet reduced in fat,²² and the other was in premenopausal women following a vegetarian diet.¹⁹ In contrast, a study performed in postmenopausal women found increased testosterone levels in association with increased levels of SHBG after 4 weeks of consuming a reduced-fat diet (lean meat, poultry, and fish compared to beef, pork, egg, and milk).¹⁵ The opposite was observed in 48 premenopausal women consuming a high-fiber and low-fat diet.¹⁷ In conclusion, no clear effect on androgens can be attributed to diet according to available results.

In summary, after a diet intervention leading to weight loss, increased SHBG levels are generally observed independent of diet composition while no clear conclusion can be drawn regarding androgen levels.

CROSS-SECTIONAL STUDIES

Sex hormone-binding globulin

Numerous cross-sectional studies have been published to examine the impact of different eating habits on plasma concentrations of sex hormones. In several of these studies,^{7,36,37} vegetarians were compared to non-vegetarians, which makes it difficult to identify the effect of a precise, isolated, nutritional compound on SHBG and sex hormone levels. Important differences in adiposity between these two types of eating habits are also generally observed, which could contribute to concomitant differences in plasma concentrations of sex hormones.

In contrast with intervention studies, more reports of cross-sectional studies of men were available. One of these studies included 696 healthy men (226 meat-eaters, 237 vegetarians, and 233 vegans) and SHBG levels were 16% higher, concomitant with a lower BMI in vegans than in meat-eaters (22.7 vs. 26.1 kg/m², respectively).³⁷ Statistical adjustment for BMI attenuated differences in SHBG levels, but the difference between meat-eaters and vegans remained significant. More precise adiposity measures, such as percent body fat or visceral adipose tissue areas were not performed in that study, which could explain the latter finding. However, an effect of diet that may be independent of adiposity differences can not be excluded in that study. Another analysis of this population was published 2 years later.⁷ In the same sample, men who had a BMI above 30 kg/m² had 45% lower SHBG values, and saturated fat intake was inversely correlated with plasma SHBG levels. Another study including 51 vegans and 57 omnivores also found a significantly lower BMI in vegans than in omnivores. In the latter study, vegans had 23% higher plasma SHBG concentrations than omnivores before and after statistical control for

BMI.³⁸ In a subset of 18 vegetarians and 22 omnivores, a significant positive correlation was found between total fat, saturated fatty acids, polyunsaturated fat, and SHBG. In the same order of idea, Longcope et al.,¹⁸ also found a negative correlation between BMI and SHBG in 1563 healthy men. The latter study observed a positive correlation between plasma SHBG levels and fiber intake. Field et al.⁹ studied 1241 middle-aged men and found that SHBG was lower in men with increasing relative BMI. More specifically, this study showed an inverse significant correlation between consumption of animal fat and SHBG levels, while a positive significant association between dietary fiber and SHBG was observed. Wu et al.³⁹ also found lower SHBG levels with higher BMI and higher weight. In general, cross-sectional studies in men found negative correlations between BMI and SHBG levels, regardless of the differences in diet composition. Although precise adiposity measures were not used in statistical adjustments, it appears that BMI differences can not explain all the differences observed in SHBG levels. It remains difficult to identify a specific nutrient that is clearly linked to SHBG levels according to available data. Moreover, little information on insulin levels was available in the studies cited.

In cross-sectional studies performed in women, the results are even less conclusive. Gates et al.⁴⁰ found that BMI was inversely correlated with plasma SHBG concentrations in 25 healthy Chinese women. In that study, SHBG was also negatively correlated with insulin. Using a 3-day dietary record, specific nutrients predicting SHBG levels could be identified after statistical adjustment for BMI. The strongest predictors of SHBG concentrations were the intake of rice, millet, and wheat.⁴⁰ A study including 640 premenopausal (153 meat-eaters, 332 vegetarians, and 38 vegans) and 457 postmenopausal (223 meat-eaters, 196 vegetarians, and 38 vegans) women found that BMI was significantly lower in vegetarians and vegans compared to meat-eaters. However, no difference was found in SHBG levels after statistical adjustment for BMI.⁴¹ Conversely, Armstrong et al.,³⁶ found that, for postmenopausal women with a similar BMI, vegetarian women had higher levels of SHBG compared to non-vegetarian women. Another study including 27 postmenopausal women (9 vegetarians, 10 omnivores, and 8 women with breast cancer) found that SHBG levels were lower in vegetarians than in omnivores, but this difference was not significant. Interestingly, in the latter study, BMI and body weight were significantly higher in the vegetarian group.⁴² In that particular sample, differences in weight and BMI were quite surprising and diverged from results usually obtained when vegetarians and omnivores are compared. Nevertheless, lower BMI values were associated with higher SHBG levels. These findings are of interest because the effect of adiposity seems more

important than the effect of diet composition *per se*. This study also found a negative correlation between protein intake and SHBG levels.⁴² Finally, a study examined the impact of dietary fiber intake on SHBG levels in 205 premenopausal women. The authors found that SHBG was significantly lower in women who consumed between 1.7 and 7 fruit portions compared to those consuming less than 0.6 portions a day,⁴³ but no association was found between intakes of vegetables or whole grains, total dietary fiber, and SHBG levels. In short, cross-sectional studies in women found divergent results and no clear conclusions can be drawn regarding the independent effect of diet on circulating SHBG levels.

Circulating androgens

Regarding androgen levels and their association with eating habits or specific nutrients, results in men are also relatively divergent. A study including 696 healthy men observed that men eating a vegan diet had higher testosterone levels.³⁷ However, in the same sample, irrespective of the type of diet, men who had a BMI above 30 kg/m² had 30% lower testosterone levels and 5% lower free-T levels in association with a reduced SHBG level, which suggests an independent impact of BMI.⁷ Another study found that in men consuming a vegan diet, free-T levels were 3% lower and total testosterone levels were 7% higher in vegans, but these differences were not significant. These results were found in association with higher levels of SHBG in vegans after statistical adjustment for BMI, age, and alcohol intake.³⁸ In contrast, Field et al.⁹ found proportionally lower 4-dione, total testosterone, and DHT with increasing relative weight. In another study by Wu et al.,³⁹ BMI and body weight were negatively associated with testosterone, free testosterone, and DHT levels. Tamimi et al.⁴⁴ found that testosterone levels were inversely correlated with total lipids and proteins, and positively correlated with carbohydrate intake, without any impact of adiposity measures. According to these studies in men, divergent results were found and no clear conclusions can be drawn regarding diet and androgen levels.

Associations between diet and androgenic status in women are also equivocal. In Chinese women, BMI was inversely correlated with SHBG levels whereas testosterone was significantly and positively associated with BMI. When looking at specific nutrients, testosterone levels were positively associated with wheat intake but inversely correlated with rice and green vegetable intakes.⁴⁰ In a study in which postmenopausal and premenopausal women were examined, American Caucasian and new immigrant Oriental women were compared. Oriental women had lower testosterone and 4-dione levels independent of menopausal status and BMI.⁴⁵ Adlercreutz et al.⁴² studied sex hormone levels in omnivores ($n = 10$)

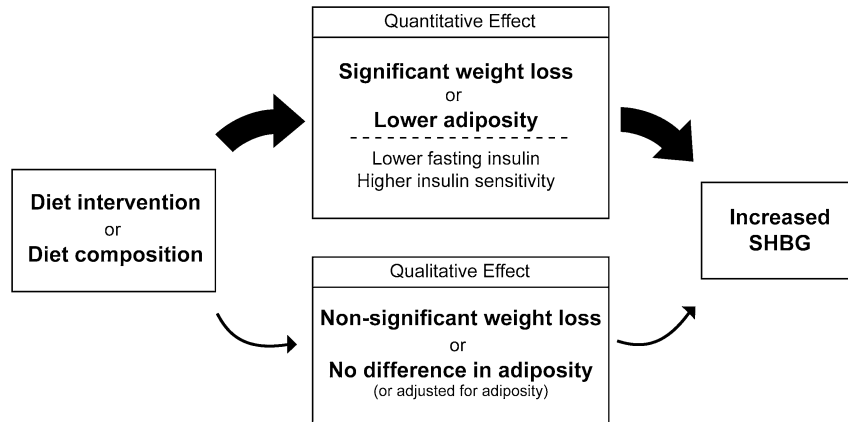


Figure 1 Pathways by which diet intervention or diet composition could impact circulating SHBG levels. The majority of studies seem to indicate that diet interventions reducing caloric intake and leading to significant weight loss increase SHBG levels, regardless of diet composition.

versus vegetarians ($n = 9$) and concluded that vegetarians had significantly higher levels of 4-dione compared to omnivores. The same study found that fat intake was positively correlated with 4-dione, testosterone, and free-T, whereas carbohydrate, grain, total fiber, and grain fiber intake showed opposite correlations with these hormones. These authors also found that protein intake was positively correlated with free-T.⁴² When no difference in BMI was observed between omnivore ($n = 10$) and vegetarian premenopausal women ($n = 10$), Goldin et al.⁴⁶ found that vegetarians had 11% higher levels of 4-dione but similar levels of testosterone. Armstrong et al.³⁶ also compared vegetarians ($n = 46$) and non-vegetarians ($n = 47$) and found no difference in plasma testosterone concentrations, despite the fact that vegetarians had higher levels of SHBG (though the difference was not significant). Finally, in 205 premenopausal women, higher dietary fiber intake and fruit consumption were significantly associated with lower 4-dione levels. In that study, testosterone levels were not measured.⁴³ In summary, no general consensus emerges from studies that have examined diet and androgen levels in both men and women.

PLAUSIBLE MECHANISMS

Our review of the literature indicates that the levels of obesity and insulin may be critical determinants of the link between diet and androgen or SHBG levels (Figure 1). Several mechanisms could explain these effects. First of all, diet could modulate SHBG levels by acting on insulin levels. As mentioned, studies showed that diets leading to weight loss and an improvement in insulinemia are associated with increased SHBG levels, especially in women with PCOS.^{11,23–25} A study by Plymate et al.⁴⁷ showed a direct effect of insulin on hepatocyte SHBG secretion.

Furthermore, Nestler et al.⁴⁸ showed that suppression of insulin release by diazoxide treatment for 10 days induced significant increases in SHBG levels in women with PCOS. These results suggest that the relationship between diet, weight loss, and low SHBG could be explained by an improvement in insulin sensitivity and/or reduced insulinemia. Second, the effect of diet on SHBG could also be explained by cortisol production. Cortisol inhibits SHBG production⁴⁹ and patients with abdominal obesity and insulin resistance are characterized by increased local cortisol production in abdominal adipose tissue.^{50,51} Elevated cortisol production could possibly explain the lower levels of SHBG associated with an elevated BMI. In addition, weight loss leading to improved cortisol homeostasis could mediate an important portion of dietary effects on SHBG. Third, plasma levels of SHBG are also regulated by androgens and estrogens.⁴⁹ An increased local conversion of androgens to estrogens or inactive androgen metabolites in an enlarged adipose tissue mass⁵² could also contribute to modulate the androgen/estrogen balance and modulate SHBG levels. With weight loss, this balance could be slightly altered, leading to an increase in SHBG levels. However, it must be kept in mind that we did not reach firm conclusions regarding the effects of diet on androgen levels. Finally, dietary fiber could contribute to explain the effect of diet on SHBG. Soluble dietary fibers have been shown to reduce postprandial glucose levels and improve insulin sensitivity.^{53,54} This improvement in glucose-insulin homeostasis could be associated with an increase in SHBG levels.

CONCLUSION

Because of the disparities between studies such as inclusion and exclusion criteria, sex and age, metabolic status

and hormonal status, sample size, length of the study, type of diet, etc., firm conclusions cannot be reached regarding the effects of diet on androgens. Generally, consistent results were found regarding SHBG levels. Reduced caloric intake leading to significant weight loss increases SHBG levels in women, regardless of diet composition. The same trend is observed in men, more particularly in obese men. When looking at cross-sectional studies, elevated weight, BMI, or adiposity is generally associated with lower SHBG levels. However, no clear association can be ascertained regarding the effect of different eating habits independent of adiposity. We could not clearly identify any nutrient consistently having a direct, independent impact on circulating androgen concentrations or plasma SHBG levels when body fatness was taken into account. In conclusion, the possibility of modulating sex hormone levels has been examined in the studies reviewed here. Consistent with epidemiological data showing that obesity has been associated with increased rates of cancers,⁵⁵ including hormone-dependent cancers such as breast⁵⁶ and prostate cancers,⁵⁷ we suggest that dietary effects can be expected if body weight, fatness, and/or insulin homeostasis are modulated.

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