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Postprandial Changes in Sex Hormones After Meals of Different Composition

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The postprandial effects of different meals on serum testosterone, serum sex hormone-binding globulin (SHBG), and free androgen index were sequentially evaluated in 15 healthy men. The isocaloric meals contained different proteins and different quantities and type of fat as a mixed meal. Four test meals were given to subjects in random order: a lean meat meal, a tofu meal (both containing approximately 20% energy from fat), and meat meals with added animal fat or safflower oil (both 54% energy from fat). Blood samples were obtained at baseline and at 2, 3, and 6 hours after each meal. There was a significant decrease in testosterone and free androgen index after both tofu and lean meat meals. The 2-hour serum testosterone and the decremental area under the curve were significantly more negative after the lean meat meal than the meat meal with added animal fat. The testosterone area under the curve was least for the high animal fat meal indicating little change from baseline. As men are postprandial for a significant proportion of the day, the lower sex hormone values after a low animal fat meal may provide long-term benefits in reducing the risk of diseases, such as prostate cancer, which appear to be sex hormone-dependent.

PROSTATE DISEASE HAS been increasingly diagnosed in many developed countries, but the etiology has not been clearly established. Lifestyle factors, such as diet, have been implicated as possible contributory factors in the development of clinically advanced stages of the disease. Populations with higher intakes of animal fat, meat, and dairy products have been observed to have higher rates of prostate disease,[1,2] while the intake of soy products in some Asian countries has been suggested to be protective.[3]

Because prostate disease is considered to be sex hormone-dependent, it has been proposed that dietary factors may influence sex hormone concentrations in a manner that may increase the risk for prostate disease.[4] A small number of intervention studies in healthy men have reported changes in the blood concentration of some sex hormones in response to different diets. Decreased circulating testosterone and androstenedione were found in 30 male subjects after changing from a high saturated fat diet to one that was low in fat with a higher polyunsaturated to saturated fat (P:S) ratio.[5] In another study, shifting from a mixed diet containing meat to a lacto-ovo vegetarian diet resulted in lower total testosterone concentrations after the vegetarian diet.[6] A diet high in fat and low in dietary fiber has also been reported to lead to a higher concentration of plasma testosterone.[7] While blood hormone measurements in these studies were performed on fasting samples in response to different diets that lasted for several weeks, there is little data available on the postprandial effects of mixed meals on sex hormone concentrations in healthy men. Yet humans are in a postprandial state for a major portion of the day, and any changes in sex hormone concentrations in response to meals may also have an influence on prostate function and development.

Data from animal experiments suggest testosterone concentrations may be acutely influenced by fasting and food intake,[8-10] and there is limited data from small studies in humans suggesting that postprandial changes in testosterone concentrations may also occur in response to a high-fat meal.[11,12] However, further study is needed to determine whether differences in the source of protein, as well as the amount and source of fat in meals, may alter postprandial sex hormone concentrations.

We conducted a study to investigate the hypothesis that different meals would have a different postprandial effect on circulating testosterone concentrations in healthy men. Comparisons were made between meals with different sources of

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Table 1. Nutrient Composition of Test Meals

	Tofu Meal	LM Meal	MAF Meal	MSO Meal
Energy (kJ)	1,588.0	1,567.0	1,691.0	1,691.0
Protein (g)	26.6	26.6	23.9	23.8
Carbohydrate (g)	49.4	46.5	22.3	22.3
Fat (g)	8.2	8.8	24.5	24.5
SF (g)	2.9	2.9	11.9	4.2
MF (g)	2.7	3.0	9.8	4.9
PF (g)	1.9	1.8	1.2	13.8
P:S ratio	0.7	0.6	0.1	3.3
Cholesterol (mg)	3.6	48.8	71.1	54.9
Protein (% energy)	28.5	28.8	24.0	24.0
Fat (% energy)	19.1	20.9	54.0	54.0
Carbohydrate (% energy)	49.9	47.5	21.1	21.1

Abbreviations: SF, saturated fat; MF, monounsaturated fat; PF, polyunsaturated fat; P:S ratio, polyunsaturated to saturated fat ratio.

protein (soy *v* meat), different amounts of saturated fat from animal sources (lean meat *v* meat with animal fat), and fat content from different sources (animal fat *v* vegetable fat as safflower oil).

SUBJECTS AND METHODS

Healthy male volunteers between the ages of 25 and 64 years were recruited through local contacts and newspaper advertisements. Men with symptoms or prior diagnosis of prostate disease or other illnesses, with excessive alcohol intake, or those on medications that may affect sex hormone concentrations were not included. The study protocol was reviewed and approved by the Deakin University Ethics Committee, and written informed consent was obtained from all the participants.

Test meals were given to each subject in random order, with at least 7 days between each test meal. The tofu meal contained 150 g tofu (raw weight, but eaten grilled) cooked with 4 g beef dripping. The lean meat (LM) meal contained an equivalent amount of protein from 80 g (raw weight) lean beef mince cooked with 2 g polyunsaturated margarine. The meat and animal fat (MAF) meal contained 90 g lean beef mince cooked with 18 g beef dripping (containing 54.5% saturated, 42.6% monounsaturated and 2.9% polyunsaturated fat). The meat with safflower oil (MSO) meal contained 90 g lean beef mince cooked with 18 mL safflower oil (containing 75.9% polyunsaturated, 14.2% monounsaturated and 9.8% saturated fat). All of the meals were seasoned with 10 g oyster sauce and served with a slice of tomato, lettuce, and a white bread roll. The levels of energy, protein, amount and type of fat, and carbohydrate were kept similar in the LM and tofu meals, with only the source of protein varying. In comparing the LM meal versus the MAF meal, the percentage of energy from fat provided 21% and 54%, respectively, and the amount of carbohydrate was adjusted to keep the amount of energy as similar as possible. The nutrient composition of the test meals was calculated using the diet analysis software Diet 1 version 4 (Xyris Software, QLD, Brisbane, Australia). All of the tofu, meat, and bread rolls used for the test meals were purchased from a single source.

Subjects were instructed to avoid strenuous exercise and to exclude all alcoholic beverages, soy products, or meat from their diet 24 hours before each experiment, and were asked to remain fasted from 10 PM on the night before each test meal. A fasting venous blood sample was obtained between 7 AM and 7:15 AM. Each volunteer was then given the test meal, which was consumed within 15 minutes. Participants then remained comfortably seated in the clinical room for 6 hours after each meal, during which period only water consumption was allowed. A

Table 2. Baseline and Postprandial Concentrations of Serum Testosterone, SHBG, FAI, Insulin, and LH After the 4 Test Meals (mean ± SEM)

	Tofu Meal (n = 15)	LM Meal (n = 15)	MAF Meal (n = 13)	MSO Meal (n = 10)
Testosterone (nmol/L)				
Baseline	15.6 ± 1.1	17.6 ± 1.8	16.2 ± 1.3	16.3 ± 1.4
2 hours	13.3 ± 0.8*	13.7 ± 1.2†	14.7 ± 1.4	13.5 ± 1.4
3 hours	13.5 ± 1.0	14.5 ± 1.1	14.9 ± 1.6	13.9 ± 1.3
6 hours	15.1 ± 1.0	14.8 ± 1.1	16.2 ± 1.5	15.2 ± 1.4
SHBG (nmol/L)				
Baseline	30.5 ± 4.3	33.0 ± 4.4	30.7 ± 4.5	32.3 ± 5.3
2 hours	32.3 ± 4.2	32.2 ± 4.2	30.0 ± 4.4	32.0 ± 5.3
3 hours	30.8 ± 4.0	30.8 ± 3.8	30.3 ± 4.6	33.8 ± 5.7
6 hours	31.7 ± 4.3	30.9 ± 4.1	30.9 ± 4.9	34.1 ± 6.1
FAI				
Baseline	67.1 ± 11.2	67.9 ± 11.3	66.1 ± 9.3	63.6 ± 10.9
2 hours	53.2 ± 8.7†	53.3 ± 8.3†	61.7 ± 10.0	50.8 ± 7.5
3 hours	55.3 ± 8.5†	56.4 ± 6.9	61.6 ± 9.4	51.7 ± 7.7
6 hours	60.3 ± 8.6	57.7 ± 7.5	65.6 ± 8.5	55.7 ± 8.4
Insulin (pmol/L)				
Baseline	66.2 ± 7.5	70.6 ± 9.1	82.0 ± 17.1	69.2 ± 14.9
2 hours	134.6 ± 42.5	196.8 ± 63.7	148.4 ± 53.4	217.1 ± 84.8
3 hours	83.3 ± 12.6	111.0 ± 46.1‡	114.0 ± 51.9§	128.8 ± 42.7
LH (mIU/mL)‖	(n = 12)	(n = 11)	(n = 11)	(n = 10)
Baseline	3.6 ± 0.3	4.2 ± 0.5	4.2 ± 0.6	3.4 ± 0.3
3 hours	4.9 ± 0.8	4.7 ± 0.5	4.9 ± 0.6	4.1 ± 0.3
6 hours	4.3 ± 0.7	4.2 ± 0.4	3.9 ± 0.4	5.2 ± 1.0

Abbreviations: LM meal, lean meat meal; MAF meal, meat with animal fat meal; MSO meal, meat with safflower oil meal.

*$P \leq .01$; †$P \leq .05$, significantly different compared with mean value at baseline.

‡$P \leq .05$; §$P \leq .01$, significantly different compared with mean value at 2 hours.

‖Analysis performed on available remaining samples.

venicatheter was inserted into an antecubital vein for collection of blood samples, and the catheter was kept open with saline. After each meal, 20-mL blood samples were collected into plain vacutainer tubes at 2, 3, and 6 hours after discarding an initial 5-mL sample. Blood samples were allowed to clot for 1 hour at room temperature and centrifuged at 2,000×*g* for 20 minutes at 4°C. Serum aliquots were immediately stored at −80°C for later analysis.

Baseline and postprandial serum samples were analyzed for total testosterone, insulin, sex hormone-binding globulin (SHBG), and luteinizing hormone (LH), and the free androgen index (FAI; testosterone concentration/SHBG concentration × 100) was calculated. Commercial radioimmunoassay kits were used to analyze serum total testosterone (Medgenix, Biosource, Fleurus, Belgium), insulin (Linco Research, St Louis, MO), and LH (DPC, Doncaster, Victoria, Australia). SHBG was analyzed using a commercial immunoradiometric kit (Spectria, Orion Diagnostica, Espoo, Finland). All samples taken from each subject were assayed in a single batch. Intraassay coefficients of variation were all less than 10%.

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences version 8 (SPSS Inc, Chicago, IL). Pearson and Spearman correlation coefficients were determined on data that had normal and non-normal distribution, respectively. The net incremental area for insulin was calculated using geometrical equations following the method used by Gannon et al,[13] as the area circumscribed by the baseline and values that were above baseline at the postprandial time points. Any areas resulting from values that were below the baseline were subtracted to obtain the net incremental area. The decremental areas for testosterone and FAI were calculated using a similar procedure.

Serum concentrations at 2, 3, and 6 hours after each test meal were compared with baseline values using repeated measures analysis of variance (ANOVA), and post hoc analysis was performed using Bonferroni adjusted comparisons. The changes from baseline values for each variable were compared between test meals (tofu *v* LM; LM *v* MAF; and MAF *v* MSO), using the paired *t* test or Wilcoxon signed rank test for normally distributed data and non-normally distributed data, respectively. A 1-sample *t* test was used to test whether the decremental areas after the meals differed significantly from 0, which represents the extrapolation of the area for the postprandial period with no changes from baseline. Data are presented as the mean ± SEM, and $P \leq .05$ was used to define statistical significance.

RESULTS

A total of 15 subjects participated in the study, but 5 subjects were unable to undertake all the test meals. Comparisons are thus given for tofu versus LM (n = 15), LM versus MAF (n = 13), and MAF versus MSO (n = 10). Subjects had a mean age of 42.8 ± 3.1 years, body weight of 77.2 ± 2.1 kg, and body mass index (BMI) of 25.4 ± 0.8 kg m^{-2}. The subjects' mean

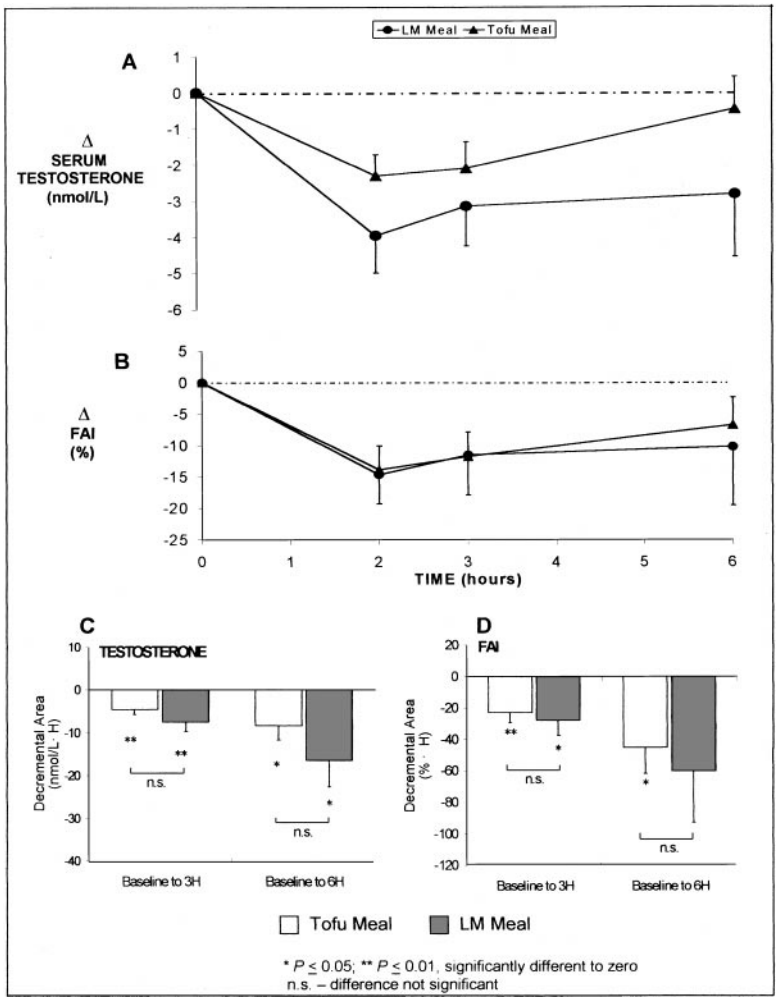

Fig 1. Changes from baseline for serum testosterone concentration (A) and FAI (B); decremental areas for serum testosterone (C) and FAI (D) after the tofu and LM meals (n = 15).

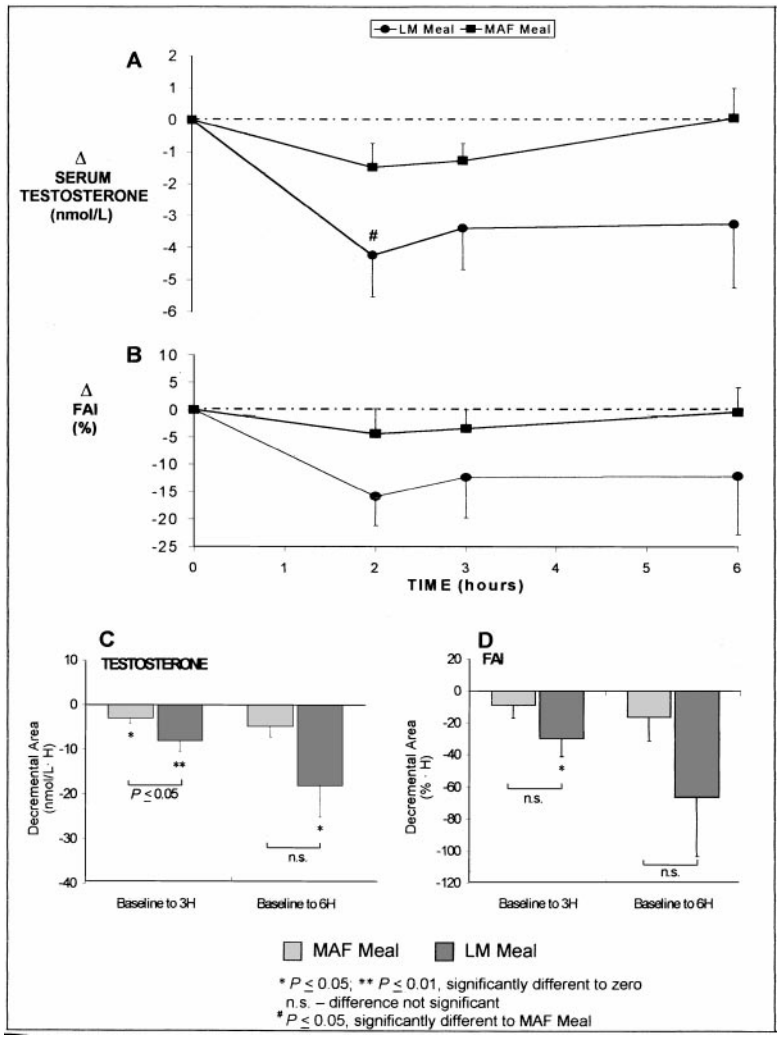

Fig 2. Changes from baseline for serum testosterone concentration (A) and FAI (B); decremental areas for serum testosterone (C) and FAI (D) after the LM and MAF meals (n = 13).

serum cholesterol was 5.4 ± 0.3 mmol/L and triacylglycerol was 1.3 ± 0.6 mmol/L. The nutrient composition of the test meals is shown in Table 1. Fasting serum total testosterone, SHBG, and the FAI were not significantly different before test meal consumption, and the values at baseline and after the 4 meals are shown in Table 2.

The postprandial relationships between serum testosterone, SHBG, and insulin were explored. There were significant correlations between the changes in testosterone and the changes in SHBG after the tofu meal (2-hour: $r = .63$, $P = .01$; 3-hour: $r = .54$, $P = .037$), the LM meal (2-hour: $r = .50$, $P = .05$), and the MSO meal (2-hour: $r = .75$, $P = .013$; 3-hour: $r = .82$, $P = .004$), but not after the MAF meal. There were no significant correlations between testosterone and insulin and between insulin and SHBG.

Tofu Versus Lean Meat (n = 15)

Mean testosterone concentration decreased significantly 2 hours after both meals (Table 2), but the difference between the 2 meals was not significant. The changes in serum levels and decremental areas under the curve for serum testosterone and FAI are shown in Fig 1. The changes in SHBG concentration were significantly more positive after the tofu meal at 2 and 3 hours ($P = .04$ and $P = .01$, respectively). The changes in insulin concentration and the incremental area were not significantly different after the 2 meals.

Lean Meat Versus Meat With Animal Fat (n = 13)

Mean serum testosterone concentration decreased significantly from baseline at 2 hours after the LM meal, in contrast to the MAF meal in which serum testosterone at this time point was not different from baseline (Table 2). The changes in testosterone at 2 hours and the decremental area for testosterone (baseline to 3 hours) were significantly more negative after the LM meal (Fig 2). The changes in SHBG, FAI, and the FAI decremental area were not significantly different after the 2 meals. The FAI decremental area (baseline to 3 hours) was significantly different from baseline ($P = .006$) after the LM meal, but not after the MAF meal (Table 2). The change in insulin concentration at 2 hours was higher after the LM meal ($P = .02$) and the incremental area for insulin after the LM meal was significantly larger than after the MAF meal (227.2 ±

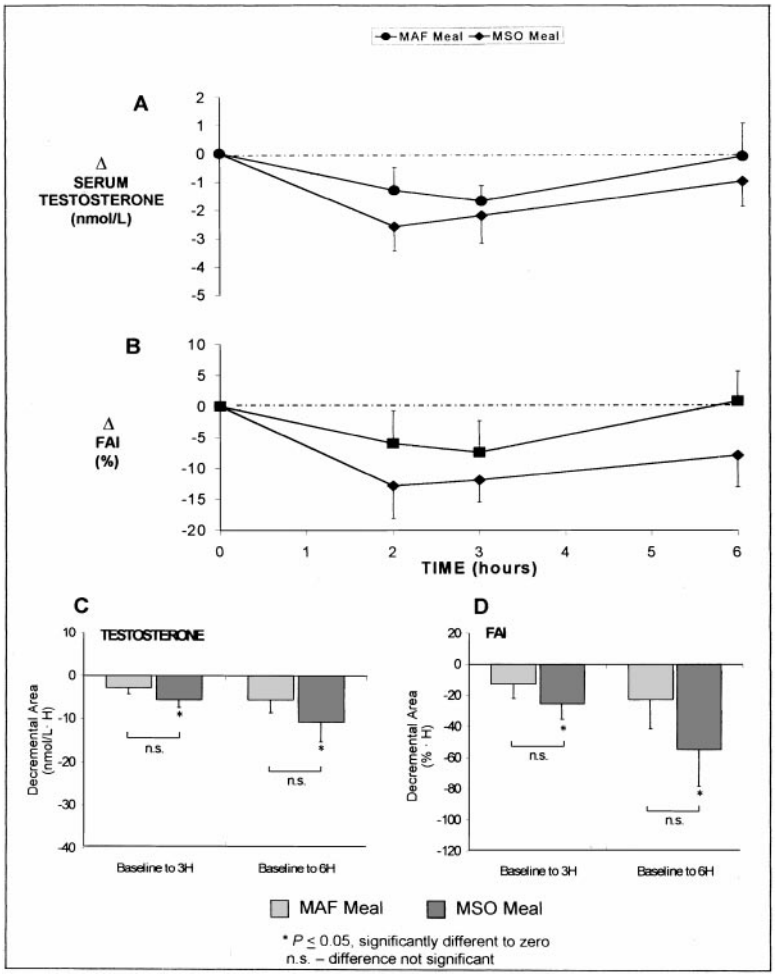

Fig 3. Changes from baseline for serum testosterone concentration (A) and FAI (B); decremental areas for serum testosterone (C) and FAI (D) after the MAF and MSO meals (n = 10).

117.2 pmol/L · h and 115.6 + 72.9 pmol/L · h, respectively; $P = .04$).

Meat With Animal Fat Versus Meat With Safflower Oil (n = 10)

Mean testosterone concentration decreased significantly after the MSO meal, but not after the MAF meal (Fig 3). The changes in SHBG were not significantly different after the 2 meals. The mean insulin value was significantly higher at 2 hours ($P = .01$) and the incremental insulin area significantly higher after the MSO meal than the MAF meal (251.7 ± 121.0 pmol/L · h and 138 ± 94.5 pmol/L · h, respectively; $P = .02$). Luteinizing hormone levels were not significantly different after any of the test diets.

DISCUSSION

The results of this study indicate that the composition of a meal may influence the serum concentration of testosterone in healthy men. Testosterone concentration decreased significantly 2 hours after the tofu, LM, and meat plus unsaturated safflower oil meals, but not after the MAF meal. Serum testosterone exhibits a diurnal rhythm.[14,15] Environmental factors such as stress, sleep, and exercise may influence this rhythm[16-18] and were kept constant in our cross-over design to reduce such confounding. Previous small studies in primates and humans have shown effects of fasting and meal consumption on blood testosterone levels,[9,11,12] suggesting food intake may influence the diurnal rhythm, whereas a non-nutritive meal does not.[12] Our results indicate the composition of the meal, particularly the amount and type of fat, influences postprandial testosterone concentrations. The mechanisms involved are uncertain, but may be due to increased hepatic clearance,[19-21] resulting from increased splanchnic blood flow after eating, as has been shown to affect progesterone.[22] Saturated and unsaturated fatty acids may affect steroid hormone secretion and metabolism differently.[23-25] As levels of LH, the main gonadotrophin that stimulates testosterone synthesis in the Leydig cells, were significantly different postprandially, increased LH-stimulated testosterone secretion is less likely to explain the difference in postprandial decrease after the MAF meal.

Although SHBG concentrations after the 4 test meals were not significantly different from baseline values, the small changes in SHBG correlated positively with the changes in testosterone after the tofu, LM, and MSO meals only and might have altered testosterone clearance rate. The lack of correlation between the changes in SHBG and testosterone after the MAF

meal may indicate a different effect on SHBG clearance and/or binding affinity by fatty acids in animal fat. Some in vitro data have suggested that different fatty acids alter binding of sex hormones to plasma proteins and influence the amount of bioavailable hormones,[26-29] with unsaturated fatty acids inhibiting protein binding more than saturated fatty acids.[28-30] Although data under physiologic conditions are inconsistent,[29-32] fatty acids have been suggested as regulators of sex hormone bioavailability.[28,31,33] A higher binding affinity of plasma proteins to sex steroids could theoretically decrease testosterone clearance and increase the blood concentration. Differing neuroendocrine and metabolic responses to food could influence hormone synthesis and secretion[34,35] and alter testosterone levels, as the serum half-life is short.[36] A role for insulin has been suggested,[37,38] but insulin, LH, and testosterone levels did not correlate closely after the test meals.

Comparison of meals with different sources of protein from tofu or LM, but with similar amounts of carbohydrate and fat, showed a significant decrease in serum testosterone from baseline after both meals, but no significant difference in testosterone response between the 2 meals. However, the net changes in SHBG at 2 and 3 hours were significantly higher after the tofu meal, resulting in a significant decrease in FAI and in bioavailable testosterone. Tofu contains isoflavones, such as genistein and daidzein,[39] which increase SHBG synthesis in in vitro experiments with liver cell cultures.[40,41] Isoflavones are present in plasma a few hours after ingestion of a soy meal,[42,43] but it is uncertain whether the isoflavone intake would have been sufficient to account for a rapid effect on SHBG synthesis,[44,45] although acute changes in circulating levels can occur due to reversible changes in tissue distribution[45] or conformational changes in SHBG.[46,47]

At least 2 diet intervention studies have reported higher fasting blood levels of testosterone in healthy men on a high-fat diet compared with a diet low in fat[5,7] after several weeks. We compared the acute effects of animal fat on testosterone responses after low- and high-fat meals and found the circulating testosterone to be higher after a high animal fat meal, probably due to the absence of the postprandial decrease associated with the other meals.

Epidemiologic studies have implicated diets high in animal fat in the development of clinically advanced prostate cancer.[48,49] A prospective study reported that elevated circulating testosterone and low levels of SHBG were associated with increased risks of prostate cancer years later.[50] The results of our study support other data that suggest dietary factors, particularly animal fat, and also soy, affect sex hormone metabolism.[5,7,33,51] Although the long-term biologic significance needs further investigation, humans are in a postprandial state for a major portion of the day, therefore, postprandial changes in sex hormone concentrations could influence prostate function and disease development. Our results suggest low-fat, soy protein, and safflower oil-containing meals could provide benefits compared with a diet containing high-fat meals. Additional studies are needed to clarify this effect of diet, particularly the mechanisms of action on total and free testosterone distribution, and the tissue uptake and metabolism in the prostate.

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