Effects of Dietary Selenium on Sperm Motility in Healthy Men

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ABSTRACT: A deficiency of dietary selenium leads to immotile, deformed sperm and infertility in rats, whereas supplementation of the diet with selenium compounds has been associated with both beneficial and deleterious effects on sperm function, depending on the chemical form of selenium. We conducted a randomized, controlled, and blinded intervention study on the effects of selenium in food on semen quality. Eleven healthy men were fed a controlled diet of foods naturally high or low in selenium for 120 days while confined in a metabolic research unit. Dietary selenium was 47 μg/d for the first 21 days, then either 13 μg/d or 297 μg/d for 99 days, resulting in significant changes in selenium concentrations in blood and semen. Seminal plasma selenium concentration increased 50% with high selenium and decreased 40% with low selenium. The fraction of motile sperm in the high-selenium group decreased by 32% by week 13 and ended 18% lower than baseline. Selenium concentra-

tions changed in seminal plasma but not in sperm, and serum androgen concentrations were unchanged in both groups, indicating this effect was neither androgen dependent nor caused by a change in the selenium supply to the testes. Serum triiodothyronine decreased and thyroid-stimulating hormone increased in the high-selenium group, suggesting that altered thyroid hormone metabolism may have affected sperm motility. Although this decrease in sperm motility does not necessarily predict decreased fertility, the increasing frequency of selenium supplementation in the healthy population suggests the need for larger studies to more fully assess this potential side effect.

Key words: Semen volume, hypothyroidism, nutrition, selenium supplementation, cancer chemoprevention.

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Selenium is an essential trace nutrient for humans and animals. Selenium deficiency has been linked to reproductive problems in rats, mice, chickens, pigs, sheep, and cattle (Combs and Combs, 1986), and supplementation with selenium has been reported to improve reproductive performance in sheep and mice (Tang et al, 1991; Van Ryssen et al, 1992). Selenium is required for normal testicular development and spermatogenesis in rats (Behne et al, 1996), mice, and pigs (Combs and Combs, 1986). Serum selenium is reported to be lower in men with oligospermia and azoospermia than in controls (Krsnjavi et al, 1992).

Selenium, in the form of selenocysteine, functions as the catalytic center in the active sites of at least 9 human enzymes, including 4 glutathione peroxidase antioxidant enzymes (Mills, 1959; Cohen and Takahashi, 1986; Zhang et al, 1989; Chu et al, 1996), 3 iodothyronine deiodinases involved in thyroid hormone metabolism (Larsen and Berry, 1995; Salvatore et al, 1996), thioredoxin reductase involved in antioxidation and signal transduction (Gladyshev et al, 1996), and selenophosphate synthetase in the selenoprotein synthesis pathway (Low et al, 1995). Many other selenocysteine-containing proteins have been reported in humans and animals, but their functions have not been established (Wilhelmsen et al, 1981; Hawkes et al, 1985a,b; Behne et al, 1995).

The selenodeiodinase enzymes (types I, II, and III iodothyronine deiodinases) control the metabolism of thyroid hormone, which is essential for the normal development (Defranca et al, 1995) and function (Latchoumycandane et al, 1997) of testes in rats. In humans, adult hyperthyroidism has been associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses to exogenous gonadotropin-releasing hormone, gynecomastia, increased sex hormone-binding globulin, and an increase in libido, whereas adult hypothyroidism has been associated with testicular resistance to gonadotropins, decreased testosterone and sex hormone binding globulin, diminished libido, and impotence, but direct effects of thyroid hormone on the testes have not been reported in adults (Jannini et al, 1995).

Phospholipid hydroperoxide glutathione peroxidase is

expressed at higher levels in rat testes than in any other tissue (Roveri et al, 1994) and is present in the head and midpiece of sperm cells (Godeas et al, 1997), where it protects the sperm from oxidative damage and serves a dual role as the mitochondrial capsule selenoprotein (Ursini et al, 1999), which is one of 3 proteins required for maintenance of the crescent structure of sperm mitochondria (Aho et al, 1996). Glutathione peroxidase activity has also been reported in human seminal plasma (Saaranen et al, 1989). Although it is difficult to deplete testes of selenium because of the organ's tenacious affinity for the element, sperm from second- and third-generation selenium-deficient rats are largely immotile and show a high incidence of sperm midpiece defects due to disorganization of the mitochondrial helix (Calvin et al, 1981).

We fed 11 men a controlled diet of conventional foods with naturally high or low selenium contents for 120 days while confined in a metabolic research unit to assess the metabolic and physiological effects of dietary selenium. In this report we present results describing the effects of dietary selenium on the male reproductive system.

Materials and Methods

Subjects

Twelve healthy men were recruited from a pool of 148 volunteer candidates who passed an initial telephone screening. Health of candidates was assessed by medical history, physical examination, semen analysis, hematological and clinical chemistry tests, psychological testing, resting electrocardiogram, hepatitis, syphilis, tuberculosis, and human immunodeficiency virus antibody tests. Tests for alcohol, tobacco, and drug use were also performed. Candidates were excluded for weight for height greater than 125% of ideal (Metropolitan Life Insurance Co, 1980); use of selenium supplements or selenium-containing shampoos; abnormal blood cell counts, clinical chemistries, or semen analysis; indications of substance abuse; habitual use of tobacco or alcohol; chronic use of medications; history of psychiatric illness; and history of thyroid disease, hepatitis, heart disease, diabetes, hypertension, or hyperlipidemia. The study protocol was approved by the Human Subjects Review Committees of the University of California at Davis and the US Department of Agriculture. The protocol was reviewed with the study volunteers and their informed consent was obtained in writing prior to the study, in accordance with the Common Federal Policy for Protection of Human Research Subjects. One subject withdrew from the study after 60 days for personal reasons unrelated to the study, and his data were not included. The 11 subjects who completed the study were aged 20 to 45 years, and had normal weight (75.5 ± 10.6 kg), height (178 ± 5.5 cm), and body mass index (23.4 ± 3.4 kg/m²).

The subjects were confined in a metabolic research unit for 120 days under 24-hour supervision by staff members. Subjects participated in two required 2-mile walks per day, and were always escorted by staff members when out of the metabolic re-

search unit and when meeting with visitors. Due to other investigations being conducted during this study, the subjects underwent frequent blood draws and other minimally invasive procedures throughout the study.

Experimental Diets and Treatments

Subjects were fed a diet composed of conventional foods, based on beef and rice as staples, plus a vitamin and mineral supplement tablet, free of selenium (Unicap M; Upjohn Co, Kalamazoo, Mich). The total diet (Table 1) contained at least 100% of the US recommended dietary allowance (RDA) for all nutrients except magnesium (56%), calcium (72%), and selenium, and approximated the composition of a typical US diet (US Department of Agriculture, 1991). All meals were consumed completely under the direct observation of staff members.

For the first 21 days, all subjects were fed a diet that provided 47 μg/d of selenium (RDA = 55 μg/d; [Panel on Dietary Antioxidants and Related Compounds, 2000]) at the average energy intake of 11.7 MJ/d to adapt the subjects to the experimental diet and to stabilize their body weights. For the remainder of the study, the energy intake of each subject was adjusted as needed to maintain body weight by increasing or decreasing all components of the diet proportionally. The subjects were randomly assigned to one of two groups after blocking into 6 pairs matched for blood selenium concentrations. For the remaining 99 days of the study, one group was fed a diet that provided 13 μg/d of selenium and the other group was fed a diet that provided 297 μg/d, at the average energy intake of 11.7 MJ/d. The selenium intake from the low-selenium diet was as low as could be achieved with foods and was lower than the minimum intake required to prevent Keshan disease, a viral cardiomyopathy associated with selenium deficiency in China (Yang et al, 1987), and the only example of selenium deficiency disease known in humans. The selenium intake from the high-selenium diet was as high as achievable, given the selenium content of the South Dakota beef used and the design goal that half the dietary selenium be from animal sources and half from plant sources, yet remained less than the maximum "oral reference dose" of 350 μg selenium/day considered safe by the US Environmental Protection Agency (EPA; Poirier, 1994) and less than the tolerable upper intake level of 400 μg/d set by the Dietary Reference Intake (DRI) Committee (Panel on Dietary Antioxidants and Related Compounds, 2000). On day 110 only (week 16), all subjects were fed the low-selenium diet and were administered an oral dose of $Na_2^{74}SeO_3$ (10 μg selenium for the low-selenium group, or 300 μg selenium for the high-selenium group) with the morning meal as part of a metabolic tracer study. Extra blood specimens were obtained the morning of day 110 before the stable isotopes were administered to avoid any "pharmacological" effects of the sodium selenite dose.

The only difference between the experimental diets was the geographic origin of the rice and beef staples, which were obtained from regions with either very high or very low soil selenium; all other aspects of the 3 diets were identical. Composite samples of each diet were analyzed for nutrient contents at a commercial laboratory (Corning-Hazelton, Madison, Wis) using standard methods (Association of Official Analytical Chemists, 1990). The selenium contents of the 3 diets were analyzed in-

Table 1. *Diet composition**

Component	Daily Intake (per 11.7 MJ)	RDA†
Protein	68.5 g (10.6% of energy)	63 g
Carbohydrate	357 g (55.0% of energy)	NA
Fat	99.2 g (34.4% of energy)	NA
Saturated fat‡	32.0 g	NA
Monounsaturated fat‡	35.7 g	NA
Polyunsaturated fat‡	25.8 g	NA
Fiber*	6.1 g	NA
Cholesterol*	253 mg	NA
Selenium (stabilization diet)	47 µg	55 µg
Selenium (low-selenium diet)	13 µg	55 µg
Selenium (high-selenium diet)	297 µg	55 µg
Iodine†	280 µg	150 µg
Calcium	572 mg	800 mg
Iron	28.3 mg	10 mg
Magnesium	195 mg	350 mg
Phosphorus	1013 mg	800 mg
Zinc	28.4 mg	15 mg
Copper	2.93 mg	1.5–3 mg§
Manganese	3.68 mg	2–5 mg§
Potassium	2645 mg	1875–5625 mg§

  * Unless otherwise indicated, values are from analyses of composites of foods from each experimental diet. Contributions from the daily vitamin and mineral supplement are included. NA indicates not applicable.

  † RDA indicates recommended dietary allowance (National Research Council Committee on Dietary Allowances, 1989).

  ‡ Dietary component estimated from food composition tables (US Department of Agriculture, 1991).

  § Estimated Safe and Adequate Daily Dietary Intake (National Research Council Committee on Dietary Allowances, 1980).

house as described below. There were no significant differences detected between the 3 diets in their contents of protein, fat, carbohydrate, energy, cysteine, methionine, iodine, mercury, cadmium, calcium, copper, iron, magnesium, manganese, molybdenum, nickel, phosphorus, potassium, sodium, or zinc (data not shown). Subjects and the analysts were blinded to which subjects were eating which diets.

Laboratory Measurements

Blood samples were collected at 0700 hours, after an overnight fast of 12 hours. Erythrocyte, serum, and plasma samples were immediately frozen and stored at −70°C until analyzed. Serum samples were refrigerated until analyzed each night at a reference laboratory (Chemzyme Plus, SmithKline-Beecham). Serum hormones were measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif). Selenium was measured by fluorescence-derivatization high-performance liquid chromatography (Hawkes and Kutnink, 1996). Protein was determined by an automated colorimetric method (Hawkes and Craig, 1990).

Semen Collections

Semen samples were obtained by masturbation during weeks 3 (baseline), 8, 13, and 17. During each week of sampling, 3 specimens were obtained, separated by 72 hours of abstinence each time. Volume was measured in all 3 specimens and averaged to give a mean volume for each week of sampling. The third specimen of each set was subjected to standard semen analysis according to World Health Organization (WHO) guidelines using the WHO strict criteria (WHO, 1992). Sperm mean forward velocity was measured by computer-assisted videomicroscopy

(Hobson Sperm Tracker; Biogenics, Napa, Calif) from videotapes prepared during the manual semen analysis of the third specimen.

Sperm Preparation

Seminal plasma and washed sperm were prepared from the first and second specimens of each set. Liquefied semen was centrifuged at $2000 \times g$ for 10 minutes at room temperature to remove sperm and the seminal plasma was aspirated and saved. Cloudy samples of seminal plasma were clarified by centrifugation at $12\,000 \times g$ for 10 minutes and the pellets were discarded. The sperm pellet was washed once with normal saline and repelleted at $2000 \times g$ for 10 minutes at room temperature. Washed sperm were resuspended in one-half the original semen volume of 50 mM Tris-HCl, 0.5% Triton X-100 pH 7.8. Sperm and seminal plasma samples were stored at −70°C until analyzed. The selenium concentrations of the first and second specimens obtained each week were averaged.

Statistical Analysis

The data were analyzed by two-way repeated measures analysis of variance, using each subject's baseline measurement as a covariate to control for the initial differences between subjects. The analyses were performed with BMDP 7.0 program 2V, Analysis of Variance and Covariance with Repeated Measures (SPSS, Chicago, Ill), using a complete model: selenium, time, covariate, and selenium × time interaction. Significant differences between groups at each time point were tested with the Student-Newman-Keuls procedure. A probability of .05 or less was considered significant.
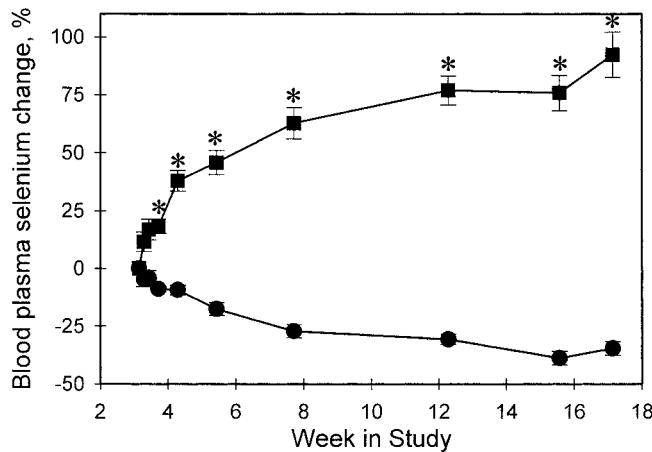
Figure 1. Changes in blood plasma selenium concentrations. Points represent the averages of the within-subject changes from baseline for subjects consuming the high-selenium diet (■) or the low-selenium diet (●). Asterisks designate the time points at which the group means were significantly different.

Results

Selenium Status

Ninety-nine days consuming the low-selenium and high-selenium diets was sufficient to significantly change selenium status in blood and seminal plasma. Selenium concentrations in blood plasma (Figure 1) began to change within 3 days of changing the diet and continued to change throughout the study. By the end of the study, blood plasma selenium concentrations had increased by 70% in the high-selenium group and decreased by 40% in the low-selenium group (Table 2). The pattern of changes in seminal plasma selenium concentration (Figure 2) was similar to the pattern observed in blood plasma, increasing by 50% in the high-selenium group and decreasing by 40% in the low-selenium group by the end of the study (Table 2). Seminal plasma selenium concentration reached a plateau by week 8, and did not change significantly thereafter. At the end of the study, seminal plasma selenium concentrations were about 20% of, and were correlated with, blood plasma selenium concentrations ($r = .68$, $P < .01$). However, the changes in selenium status were not uniform throughout the body. Erythrocyte selenium concentration increased by 65% in the high-selenium group and decreased by 37% in the low-selenium group. On the other hand, selenium concentrations in sperm, whether expressed as simple concentrations, as specific concentrations per mg of protein (shown in Table 2), or as total selenium per ejaculate, did not change significantly in either group, nor were there any significant differences in sperm selenium between groups.

Semen Quality

The fraction of motile sperm decreased by an average of 32% in the high-selenium subjects at week 13 (Figure 3), but ended only 17% lower than the baseline value at week 17 (Table 3). Sperm motility increased by an average of 10% in the low-selenium group at week 13, but was no longer significantly different from baseline by

Table 2. *Effects of low-selenium and high-selenium diets on selenium and serum hormone status*

Parameter	Low-selenium Diet		High-selenium Diet		Statistical Analysis*		
	Baseline value† (Mean ± SD)	Ending Value‡ (Mean ± SD)	Baseline Value (Mean ± SD)	Ending Value (Mean ± SD)	Se, P	Time, P	Se × Time, P
Blood plasma selenium, mg/L	0.13 ± 0.02	0.08 ± 0.02	0.12 ± 0.02	0.25 ± 0.04	.0001	.0006	.012
Erythrocyte selenium, mg/L	0.160 ± 0.009	0.116 ± 0.011	0.168 ± 0.024	0.278 ± 0.021	...	.05	.01
Seminal plasma selenium, µg/L	52 ± 17	33 ± 11	43 ± 11	63 ± 15	.004	...	...
Sperm selenium, ng/mg protein	4.5 ± 1.7	5.1 ± 2.6	4.3 ± 2.2	3.4 ± 0.9	...	...	...
3,3',5-triiodothyronine (T$_3$), nmol/L	1.57 ± 0.25	1.64 ± 0.16	1.82 ± 0.36	1.57 ± 0.07	.013	...	.048
Thyroid-stimulating hormone, mU/L	1.69 ± 0.30	1.77 ± 0.46	2.25 ± 0.81	2.96 ± 1.05	...	.011	.031
Total testosterone, ng/dL	676 ± 193	633 ± 197	576 ± 194	669 ± 257	...	...	...
Free testosterone, pg/mL	33 ± 5.5	29 ± 4.7	26 ± 6.9	31 ± 12	...	.020	...
Follicle-stimulating hormone, µU/mL	3.3 ± 3.0	3.4 ± 3.0	2.7 ± 1.4	2.7 ± 1.4	...	...	...
Luteinizing hormone, µU/mL	1.6 ± 0.6	2.4 ± 0.6	2.0 ± 1.0	2.3 ± 0.9	...	...	...
Prolactin, ng/mL	17 ± 4.4	16 ± 3.4	12 ± 6.8	16 ± 9.7	...	...	...
Estradiol, pg/mL	26 ± 9.4	29 ± 17	19 ± 8.2	25 ± 17	...	...	...
Progesterone, ng/mL	0.99 ± 0.22	0.93 ± 0.23	0.93 ± 0.36	0.84 ± 0.16	...	...	...

* Analysis of variance and covariance with repeated measures, baseline values as covariates, BMDP Program 2V. Se indicates grand means different between groups; time, ending different from baseline; and Se × time interaction, groups diverge over time.
† Single measurements in blood on day 22 or average selenium in the first and second semen specimens obtained during week 3.
‡ Single measurements in blood on day 110 or average selenium in the first and second semen specimens obtained during week 17.
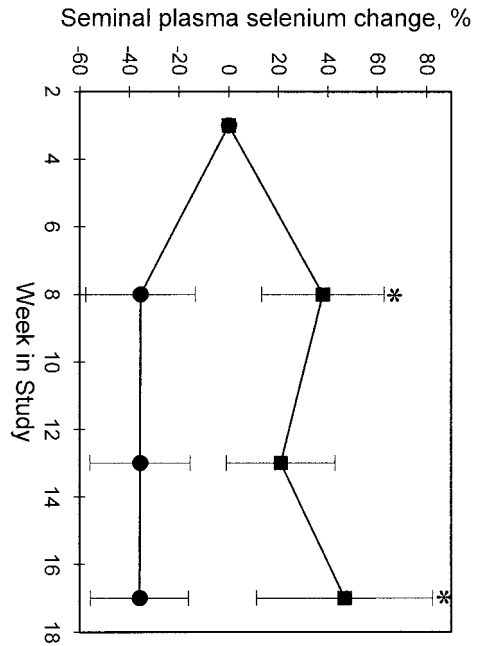
Figure 2. Changes in seminal plasma selenium concentrations. Points represent the averages of the within-subject changes from baseline for subjects consuming the high-selenium diet (■) or the low-selenium diet (●). Asterisks designate the time points at which the group means were significantly different.

week 17. The maximum effect of dietary selenium was observed at week 13, when the fraction of motile sperm in the low-selenium group was 50% greater than in the high-selenium group. There was a large and highly significant decrease in the concentration and total number of sperm in both groups during the study (Table 3). The average sperm concentration of the 11 subjects decreased gradually from 137 million/mL to 65.6 million/mL, and the average number of sperm per ejaculate decreased from 436 million to 200 million, with no significant differences between groups. Mean forward velocity decreased by an average of 16% in the 11 subjects (Table 3), but was not significantly different between groups. Similarly, the abundance of headless forms of sperm decreased by al-
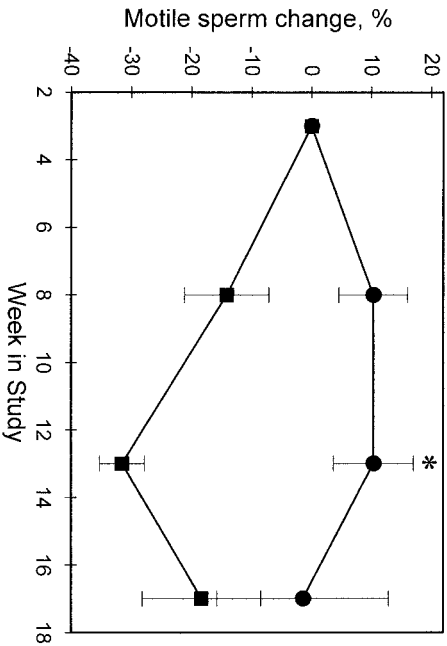

Figure 3. Changes in the fraction of motile sperm. Points represent the averages of the within-subject changes from baseline for subjects consuming the high-selenium diet (■) or the low-selenium diet (●). Asterisks designate the time points at which the group means were significantly different.

Table 3. Effects of low-selenium and high-selenium diets on semen quality

| | Low-selenium Diet | | High-selenium Diet | | Statistical Analysis* | | |
Parameter	Baseline Value† (Mean ± SD)	Ending Value‡ (Mean ± SD)	Baseline Value (Mean ± SD)	Ending Value (Mean ± SD)	Se, P	Time, P	Se × Time, P
Sperm concentration, million/mL	153 ± 123	77 ± 39	119 ± 46	52 ± 21	. . .	.045	. . .
Semen volume, mL§	3.6 ± 2.7	3.3 ± 1.8	3.4 ± 1.8	3.0 ± 1.2	. . .	. . .	. . .
Sperm total number, millions	406 ± 307	276 ± 260	472 ± 376	109 ± 15	. . .	.021	. . .
Motile sperm, fraction	0.542 ± 0.086	0.532 ± 0.196	0.588 ± 0.161	0.488 ± 0.193	.031	. . .	.010
Progressive sperm, %	90.3 ± 8.3	74.7 ± 18.8	81.6 ± 16.0	78.8 ± 15.1	. . .	. . .	. . .
Mean forward velocity, m/s	51.2 ± 5.6	40.6 ± 10.8	46.7 ± 10.0	42.0 ± 8.8	. . .	.026	. . .
Oval morphology, %	4.7 ± 1.0	13.0 ± 12.7	6.0 ± 2.0	6.2 ± 4.8	. . .	. . .	. . .
Tapered morphology, %	42.2 ± 16.0	39.0 ± 18.0	48.0 ± 8.7	49.2 ± 13.9	. . .	. . .	. . .
Amorphous morphology, %	34.5 ± 13.6	35.5 ± 19.6	28.8 ± 9.5	28.6 ± 9.7	. . .	. . .	. . .
Tail defects, %	1.8 ± 2.6	0.3 ± 0.8	3.0 ± 2.5	1.6 ± 2.2	. . .	. . .	. . .
Headless sperm, %	5.7 ± 4.9	3.0 ± 3.9	5.4 ± 3.0	1.2 ± 1.8	. . .	.028	. . .
Tailless sperm, %	1.0 ± 0.9	3.8 ± 3.9	0.8 ± 1.3	9.0 ± 9.2	. . .	.021	. . .

* Analysis of variance and covariance with repeated measures, baseline values as covariates, BMDP Program 2V. Se indicates grand means different between groups; time, ending different from baseline; and Se × time interaction, groups diverge over time.
† Value from semen analysis of third semen specimen obtained during week 3.
‡ Value from semen analysis of third semen specimen obtained during week 17.
§ Average of semen volumes of all three specimens during week 3 or week 17.
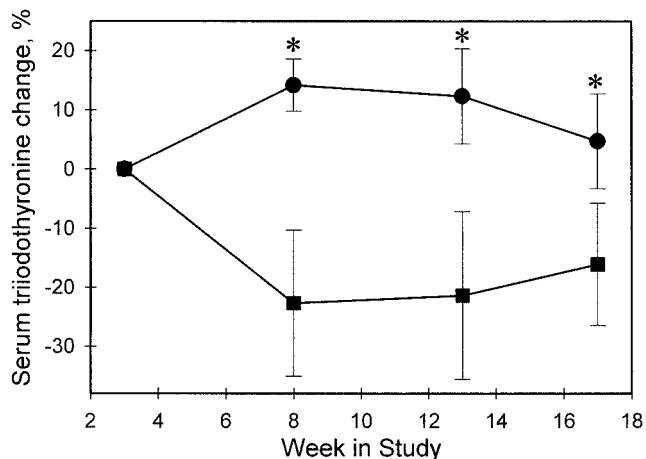
Figure 4. Changes in serum T_3 concentrations. Points represent the averages of the within-subject changes from baseline for subjects consuming the high-selenium diet (■) or the low-selenium diet (●). Asterisks designate the time points at which the group means were significantly different.

most two-thirds in both groups, whereas the abundance of tailless forms increased, again with no significant differences between groups.

Serum Hormones

By week 8, serum $3,3',5$-triiodothyronine (T_3) had increased an average of 14% in the low-selenium subjects and decreased an average of 23% in the high-selenium subjects (Figure 4), and remained significantly different between groups throughout the study. Serum T_3 ended 8% higher on average in the low-selenium subjects and 11% lower on average in the high-selenium subjects. Serum thyrotropin increased significantly by 32% over its baseline concentration in the high-selenium group but did not change significantly in the low-selenium group (Table 2). There were no significant changes in the serum levels, nor any significant differences between groups in free or total testosterone, FSH, LH, prolactin, progesterone, or estradiol.

Discussion

This appears to be the first report of dietary selenium directly affecting sperm motility in humans. However, there are several reports in the literature associating high seminal plasma selenium with impaired sperm motility in humans (Bleau et al, 1984; Takasaki et al, 1987; Hansen and Deguchi, 1996). Supplementation of rat diets with levels of selenium approximately 4 times higher than was used in the present study has also been reported to cause a decrease in sperm motility (Kaur and Parshad, 1994).

Severely selenium-deficient rats have lowered serum testosterone concentrations (Behne et al, 1996). However,

we did not observe any significant changes in serum androgens in either group, perhaps because of the much smaller changes in selenium status in our study. The lack of serum androgen changes in the present study indicates the effect of dietary selenium on sperm motility was independent of the pituitary-testes hormonal axis. Our observation that sperm selenium concentrations were unchanged shows that dietary selenium's effect was also not due to increased selenium in sperm, and implies that testis selenium was also unchanged. This is consistent with observations from rat studies in which the selenium content of testes was unchanged by dietary selenium deficiency or excess (Behne et al, 1988). A change in spermatogenesis therefore seems an unlikely explanation for this effect of selenium on motility, as neither serum androgens nor testis selenium metabolism were perturbed.

Although seminal plasma selenium increased by almost half, there is no known mechanism to explain how high selenium concentrations in seminal plasma could decrease sperm motility. Selenium toxicity seems unlikely as the intake of 297 μg/d used in this study was less than the oral reference dose of 350 μg/d considered safe for lifetime consumption by EPA (Poirier, 1994) and was well under the tolerable upper intake level of 400 μg/d set by the DRI Committee (Panel on Dietary Antioxidants and Related Compounds, 2000). It is possible that the administration of pure sodium selenite on day 110 for the tracer study could have affected sperm motility measured during week 17 (days 111–117). However, the changes in sperm motility were already significant at week 13, before the stable isotopes were administered, and the apparent motility changes between week 13 and week 17 were not statistically significant in either group.

Because seminal plasma selenium originates from epithelial secretions of the accessory sex glands (prostate gland, seminal vesicles, and epididymis), the changes in seminal plasma selenium indicate that the selenium supply to these glands changed with dietary selenium. Because sperm selenium (and by inference testis selenium) and serum androgens did not change, the effect of selenium on motility was most likely mediated by secretions from the accessory sex glands, either during sperm maturation or at ejaculation. Although there is little evidence to support a direct toxic effect of selenium in seminal plasma on sperm motility, there are many examples of factors present in seminal plasma that modulate sperm motility: fructose, which supplies fuel for respiration; angiotensin II (O'Mahony et al, 2000); calcium (Kilic et al, 1996); relaxin (Lessing et al, 1986); and epididymal motility inhibitor proteins (Turner and Giles, 1982; Turner and Reich, 1987), to name a few. More work on the forms and functions of selenium in semen and the accessory sex glands is required to understand how an increased supply of selenium might lead to decreased sperm motility.

Serum T_3 levels decreased within 23 days of starting the high-selenium diet, with a corresponding increase in serum thyrotropin, suggesting establishment of a subclinical hypothyroid state in that group. Although the decrease in circulating T_3 concentrations was quite modest, the positive response of thyrotropin in the high selenium group confirms the presence of a physiologically hypothyroid state. It is tempting to speculate that the decreased sperm motility observed in this study may have been related to this subclinical hypothyroid state. The pattern of changes in sperm motility (Figure 3) and T_3 (Figure 4) are similar, with the maximum change in T_3 at week 8 preceding the maximum change in motility at week 13.

The literature on thyroid hormone and sperm function is consistent with a role of thyroid hormone in the reduction of sperm motility by dietary selenium. Men with hypothyroidism have been reported to have lower sperm motility than euthyroid controls (Corrales-Hernandez et al, 1990) and thyroxine replacement in men with hypothyroidism is reported to improve sperm motility (Kumar et al, 1990). There is ample evidence that thyroid hormone is essential to the normal development of the testes in the neonate (Cooke et al, 1994; Defranca et al, 1995; Palmero et al, 1995; Hardy et al, 1996), and there is at least one report that thyroid hormone acts on the neonatal testes by regulating the expression of estrogen and androgen receptors in Sertoli cells (Panno et al, 1996). There are also reports of proteins in mouse kidney (Meseguer and Catterall, 1990; Sole et al, 1996) and rat liver (Dillmann et al, 1977) whose expression is regulated by both thyroid hormone and androgens. Because the accessory sex glands are developmentally related to the kidneys it is reasonable to speculate that thyroid hormone may also modulate the androgen responses of these organs as well. Such a mechanism would help explain how sperm motility was decreased without any significant changes in the levels of testosterone or other reproductive hormones. Although our observations are consistent with involvement of thyroid hormone, other mechanisms cannot be excluded.

In addition to the effects of dietary selenium on sperm motility, we also observed an overall decrease in sperm production in both groups, with sperm concentration and total sperm decreasing by more than 50% during the study. We could not identify any aspect of the diet, nor any change in the health status of the subjects that could account for such a large decrease; in fact, the overall health of the subjects seemed to improve during the study, as is typical in our metabolic studies. The decreased sperm production was not associated with a change in free or total testosterone, or any other reproductive hormone measured. Because the baseline semen specimens were obtained during the first week of May and the final specimens were taken during the first week of August, a plau-

sible explanation for the decreased sperm counts might be the seasonal variation in human sperm production, which can be as great as 50% and is reported to peak in late winter or spring and to be at a minimum in late summer (Tjoa et al, 1982; Spira, 1984; Spira and Ducot, 1985; Levine et al, 1988; Reinberg et al, 1988; Politoff et al, 1989; Saint Pol et al, 1989; Sood et al, 1993). It may also be relevant that record high temperatures occurred in San Francisco during 1993 on July 31, August 1, and August 2, the week immediately preceding the final set of semen collections, as there have been some reports that the annual variation of human sperm counts is related to variations of air temperature (Sood et al, 1993; Lerchl and Nieschlag, 1997).

Our observation that a high-selenium diet led to decreased sperm motility points to the possibility that high selenium intakes might be associated with impaired male fertility. Because of the small number of subjects in this study, the results must be interpreted with caution. Replication of these observations in larger numbers of subjects is required to lend confidence to our interpretations. Because recent reports of selenium's cancer protective effects in humans (Clark et al, 1996) may lead to increased usage of high-dose selenium supplements, it is important to establish if the observations we made in the metabolic research unit are relevant to free-living men consuming selenium supplements. Because we did not observe any change in selenium content of sperm in 14 weeks, future studies should include several complete cycles of spermatogenesis to ensure the complete effects of dietary selenium on semen quality are observed.

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