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Different Bioavailability in Humans of Wheat and Fish Selenium as Measured by Blood Platelet Response to Increased Dietary Se

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ABSTRACT

The bioavailabilities of selenium (Se) from Se-rich fish species and Se-rich wheat were compared in a study involving 32 healthy volunteers. Initial serum Se values were 109 ± 16 μg/L (mean ± SD). For 6 wk, one group (n = 11) included Se-rich bread in their diet, bringing daily average intake of Se up to 135 ± 25 μg/d. Another group (n = 11) consumed Se-rich fish daily (average Se intake: 115 ± 31 μg/d), whereas the control group (n = 10) ate their normal diet, providing 77 ± 25 μg Se/d. Serum Se increased by 17% ($P < 0.01$), and platelet Se increased by 30% ($P < 0.01$) in the wheat group. Although platelet Se decreased by 11% in the fish group, no changes in serum and platelet Se in the fish or control group reached statistical significance. Glutathione peroxidase (EC 1.11.1.9; GSH-Px) activity in serum and platelets did not change during the study, nor did platelet mercury (Hg) content. Since the dietary intake of Hg, arsenium (As),

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and fatty acids could not satisfactorily explain the lack of response in the fish group, the results are indicative of low bioavailability of fish Se in humans. At present, wheat Se seems to be the most important factor contributing to the body stores of Se in this study population.

Index Entries: Selenium; fish selenium; wheat selenium; bioavailability; mercury; arsenium; humans.

INTRODUCTION

Since the initial reports of Robinson et al. and Schrauzer and White (*1,2*) about an association between selenium intake and selenium concentrations in blood components and tissues, several similar studies have been carried out (*3–7*). Generally, the results indicate the same overall pattern: A clear, but not necessarily linear, association between selenium intake and indicators of Se status is observed, the connection being particularly strong in Se-depleted individuals, but often less expressed at higher selenium levels (*8,9*).

Within this general pattern there are, however, striking differences. For instance, when national or regional mean values for plasma Se and dietary Se intake are plotted against each other, variations are found that cannot be solely the result of environmental factors or random statistical effects. The Norwegian blood values, for instance, are among the highest in Europe, in spite of a modest dietary intake and an almost negligible environmental exposure to selenium (*8*). Moreover, Norwegians with a high-Se intake from fish consumption had only marginally elevated blood levels (*10*). On the other hand, studies with subjects living in seleniferous regions or receiving Se supplementation have demonstrated that an approximately linear connection between intake and blood levels may persist up to subtoxic intake levels (*11,12*).

Among the possible explanations for these variations, four main issues have been discussed:

1. The tissues get saturated with selenium, and the variations reflect different detoxification/excretion conditions. The saturation of glutathione peroxidase (EC 1.11.1.9; GSH-Px) can be considered an example of this (*4,8,9*).
2. Different forms of selenium in foods have different bioavailabilities. This is well known, particularly from animal studies, but there has been little investigation of the implications for the Se nutrition of populations (*13*). The observed connections between intake and status might seem to indicate that the question is primarily of academic interest.
3. Interactions with heavy metals (e.g., arsenium and mercury), their complexes, and (possibly) other compounds, as demonstrated in numerous animal studies (*14–17*), may also take place in humans.

4. Environmental and health conditions influence the selenium status, as demonstrated by lowered Se levels in oil industry workers and rheumatoid arthritis patients (*18–20*).

The present study was designed to provide more information on issues 1–3, particularly to see whether differences in bioavailability might be important in humans with relatively high serum-Se levels, like the Norwegian. To the authors' knowledge, this is the first study to assess directly the differential effects of wheat and fish, two important "Se-food" items, on selenium status in humans.

METHODS

Subjects

Thirty females and two males, aged 21–56 yr, volunteered to participate in the Se-bioavailability study. They were all students or employees at the Institute for Nutrition Research, University of Oslo. They had not taken mineral-containing supplements within 3 mo before the start of the study. They were all healthy, and none were pregnant, lactating, or using any type of medication. Four of the participants used oral contraceptives. Only two of them smoked. The participants were living at home. They were encouraged to maintain their usual daily routines and, apart from the fish group, dietary habits. Initial serum, platelet, and urinary Se levels, serum and platelet GSH-Px-activity and Hg levels, body mass index, age, and smoking habits are shown in Table 1.

Experimental Design

The intervention period lasted for 6 wk. The subjects were randomized into three groups. The wheat group (n = 11) consumed Se-rich bread providing 70 μg Se daily apart from Sundays. The fish group (n = 11) consumed a fish-rich dinner daily (apart from Sundays), providing about 70 μg Se from the fish alone. The control group (n = 10) ate their normal diet during the study.

The groups were matched for serum Se values according to measurements made 2 mo before the start of the study. Because of the students' traveling in their summer holidays, differences (NS) developed during the last 2 mo (Table 1).

Samples

Blood samples, drawn by venipuncture in the morning after a 12-h fast, were taken from the participants at weeks −8, 0, 3, and 6. Samples for trace element analysis were drawn into Vacutainer® tubes manufactured for trace element analysis (no additives) (Becton Dickinson Vacutainer Systems Europe).

Table 1
Initial Values of Serum Selenium, Platelet Se, Urine Se, Platelet Mercury, Serum and Platelet Glutathione Peroxidase Activity, Body Mass Index (BMI), and Age in Each Group (Mean Values and Standard Deviations)[a]

	Wheat group, $n = 11$		Fish group, $n = 11$		Control group, $n = 11$	
	mean	SD	mean	SD	mean	SD
Body mass index	20	2	21	2	21	2
Age	29	10	31	10	24	2
Serum Se (μg/L)	107	15	117	16	104	15
Platelet Se (μg/L)	675	100	815	150	660	240
Urine Se (μg/D)	46	14	42	14	41	17
Platelet Hg (μg/L)	78	36	64	25	60	29
Serum GSH-Px (U/g prot)	0.55	0.08	0.56	0.11	0.57	0.10
Platelet GSH-Px (U/g prot)	10.7	2.9	11.6	1.7	9.0	3.1

[a]No significant differences among the groups.

Blood for platelet isolation was drawn into Vacutainer® tubes containing ACD-A (citric acid—trisodium citrate—dextrose) as anticoagulant and prostaglandin E_1 to prevent activation of the platelets. The platelets were isolated by iodinated gradient density centrifugation, as described earlier (*21*).

The number of platelets and their volume distribution were determined by an electronic impedance counter (147C Thrombocyte Counter; Analysis Instrument AB, Stockholm, Sweden). The total volume of the platelets in the platelet sample was determined by multiplying platelet number by mean platelet volume. Urine samples were quantitatively collected for three consecutive days: initially, and at weeks three and six.

The Diets

Whole-grain wheat containing 10 mg/Se/kg on analyses was obtained from R. Marts, Bonesteel, SD, USA. The wheat was ground, mixed with appropriate amounts of ordinary Norwegian flour, and baked into bread giving 70 μg Se/90 g of bread (three slices).

Preexperimental investigations and analysis showed trout (*salmo trutta f. lacustris*), mackerel (*scomber scombrus*), wolf-fish (*anarhichas lupus*), rosefish (*sebastes marinus*), and haddock (*gadus aeglefinus*) to be the most Se-rich species available on the Norwegian market. Eating approx 250 g of these fish/d provided each participant with 70 μg Se from the fish alone. In order to be able to consume their fish dinner, many of the fish-eaters had to skip lunch. Thus, their intake of bread, the basis of a typical

Norwegian lunch, was decreased in the experimental period and, consequently, also decreased their normal wheat selenium intake.

The 32 participants collected double portions of all food and liquid intake for four consecutive days in week three or four of the study. Weighed food records were obtained simultaneously.

Analytical and Statistical Methods

Diet serum, and urine Se, and diet As were analyzed by atomic absorption spectrometry and a hydride generator system (Varian AA-1475, VGA-76) after digestion in a mixture of nitric and perchloric acid. The aliquot taken for As analysis was reduced (As^{V} to As^{III}) by addition of Na-I prior to analysis (*22,23*).

Platelet and diet samples for neutron activation analysis were freeze-dried in quartz ampules. After heat sealing, the ampules and appropriate standard solutions were irradiated for 3 d in the reactor JEEP II, Kjeller, Norway, at a thermal neutron flux of $1.2 \cdot 10^{13}\ n\ s^{-1}\ cm^{-2}$. The concentrations of Se and Hg were determined in the samples as described previously (*21*). Certified reference material of human mixed diet supplied by the International Atomic Energy Agency (IAEA), Vienna, was used for quality control. The results obtained were in close agreement with certified concentrations.

GSH-Px was measured by a modification of the coupled assay of Paglia and Valentine (*24*), with cumene hydroperoxide as substrate. The results are expressed as μkat/L/g protein. The content of dietary energy and fatty acids was calculated according to Norwegian Tables of Food Composition (*25*) by the data program "Fiber" (T. A. Ydersbond/ Norwegian Dietetic Association, Oslo).

Within groups, the changes in the variables were tested for significance by paired *t*-test. Means for the three groups were subjected to one-way analyses of variance and compared by Duncan's multiple-range test. The tests were carried out by SPSS/PC+ (SPSS-Pc + Inc, Chicago, IL, USA). $P < 0.05$ was considered statistically significant. The results are expressed as means and standard deviations, apart from the figures where results are expressed as means with their standard errors.

RESULTS

The energy, Se, fatty acid, As, and Hg contents of the diets are given in Table 2. There was no difference in total energy intake among the groups. The wheat and fish groups had a significantly higher Se intake than the control group ($P < 0.05$). The intake of marine fatty acids (total *n*-3 fatty acids) was significantly higher in the fish group ($P < 0.01$). The average daily Hg intake was found to be significantly higher (18 ± 5.5 μg/d, $P < 0.01$) for the fish group than for the wheat (2.2 ± 1.8 μg/d) and

Table 2
Dietary Intake of Selected Nutrients
(Mean Values and Standard Deviations for Each Group)

	Wheat group, $n = 11$		Fish group, $n = 11$		Control group, $n = 11$	
	mean	SD	mean	SD	mean	SD
Energy (MJ/d)	7.9	1.4	8.4	1.6	8.2	1.3
Se (μg/d)	135^a	25	115^a	31	77^b	25
Hg (μg/d)	2.2^a	1.8	17.9^b	5.5	3.1^a	2.5
As (μg/d)	139^a	175	806^b	405	101^a	33
Marine fatty acids (total $n - 3$) (g/d)	0.93^a	0.37	2.63^b	0.87	0.78^a	0.33

^{a,b}Values with different superscript letters are significantly different ($P < 0.05$; Duncan's multiple-range test).

control groups (3.2 ± 2.5 μg/d). A similar significant difference was seen between the As intake of the fish group (806 ± 405 μg/d) and the wheat (139 ± 175 μg/d) and control groups (101 ± 33 μg/d).

Serum Se increased 17% ($P < 0.01$) in the wheat group and 3% (NS) in the fish group, but decreased 3% (NS) in the control group (Fig. 1) during the 6-wk intervention period. Platelet Se increased 30% in the wheat group ($P < 0.01$), whereas it decreased 11% in the fish group and 3% in the control group (Fig. 2). Urine Se increased 65% ($P < 0.01$) in the wheat group and 46% ($P < 0.01$) in the fish group, whereas it decreased 12% (NS) in the control group (Fig. 3). This represents 56, 54, and 47% of the selenium intake in the three groups, respectively. GSH-Px values did not change in serum or in platelets in any of the groups during the study, nor did serum and platelet Hg content.

DISCUSSION

This study demonstrates that differences in bioavailability may explain much of the observed variations in the relation between selenium intake and status. Thus, it demonstrates that findings like those of Swanson and coworkers (*11*), who observed a strong relation between intake and status in a high-selenium area, should not be indiscriminatingly applied to general populations.

In the fish group, the minimal responses in serum and platelet Se levels (Figs. 1 and 2) confirm earlier observations from Norway, where communities with a high fish consumption had only 5–10% higher serum Se values than the average population (*9*). The trend toward lower platelet Se in the fish group may reflect the effect of substituting some wheat Se by fish Se, since some of the participants reduced or omitted their lunch to be able to consume the "big" fish dinner.

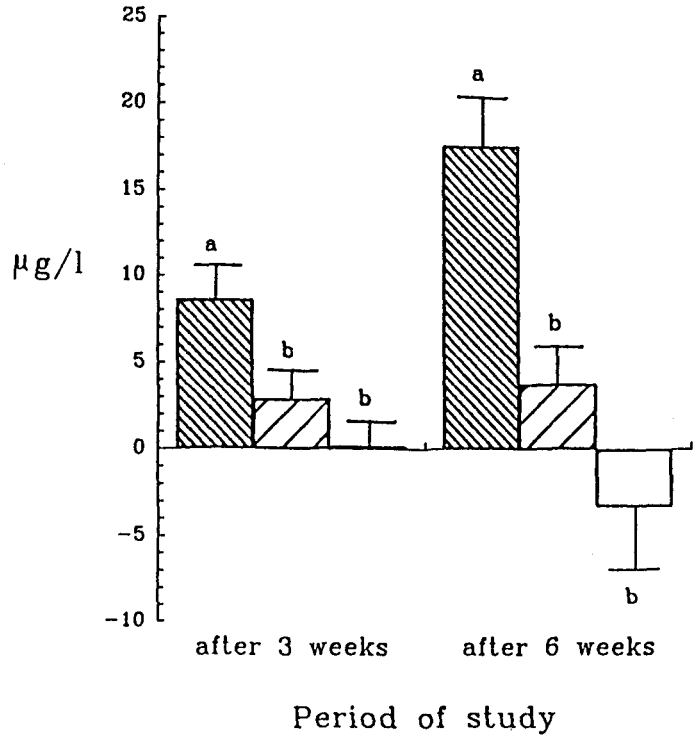

Fig. 1. Changes in serum selenium levels in the three groups studied: the wheat group (▨), fish group (▨), and control group (□). Points represent mean changes with their standard errors represented by vertical bars. Points at any given action week with different lowercase letters were significantly different ($P < 0.05$; Duncan's multiple-range test). For details of dietary treatments, *see* p. 232.

The marked platelet response to supplementation in the wheat group is at variance with the findings of Wang and Kiem (*26,27*), who observed a strict regulation of platelet Se. They found lower Se values than those found in this study (466 vs 800 μg/L wet wt), but this may be owing to methodical differences. Therefore, one cannot exclude the possibility of bioregulation on the basis of the present results, but they indicate that platelet selenium varies in the same manner as is observed in other tissues.

Several selenium compounds have failed to raise plasma, serum, or whole-blood Se levels of relatively replete individuals, in spite of urine analysis indicating good absorption (*7,8*). This is not in itself a proof of low bioavailability, since there may be little correlation between liver or plasma levels and the selenium levels in target organs, e.g., the thyroid gland (*28*). However, since the platelets are considered one of the main

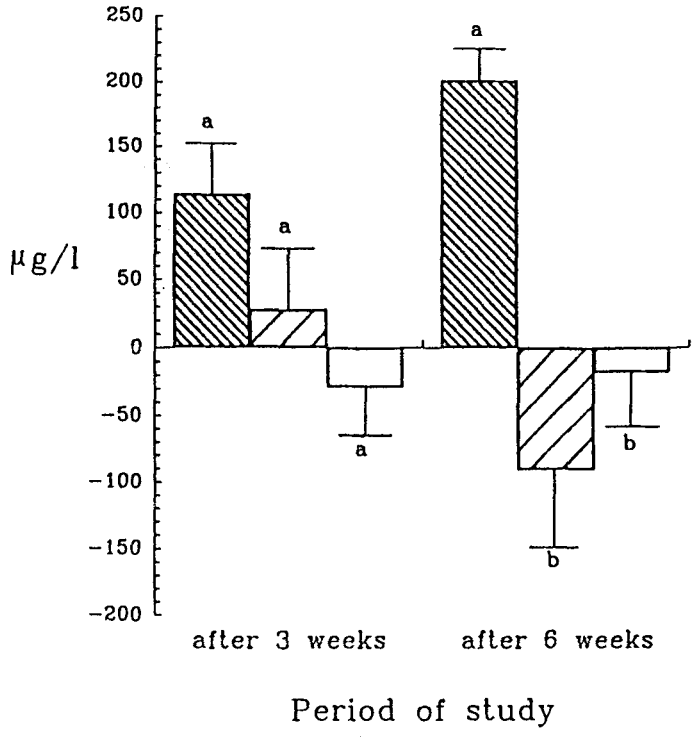

Fig. 2. Changes in platelet selenium levels in the three groups studied: the wheat group (▨), fish group (▨), and control group (□). Points represent mean changes with their standard errors represented by vertical bars. Points at any given action week with different lowercase letters were significantly different ($P < 0.05$; Duncan's multiple-range test). For details of dietary treatments, *see* p. 232.

targets of selenium in the body, the failure of fish Se to raise the selenium here is a strong indication of low bioavailability.

If the bioavailability of fish selenium in general is low, some possible explanations may be:

1. It is not well absorbed, possibly because of heavy metal interactions.
2. Heavy metals in fish, mainly mercury and arsenic, interact with selenium postabsorptionally.
3. It occurs in forms like selenonium compounds or in seleno—sulfur bonds, which are poorly available.
4. A high-methionine content in the diet reduces deposition of methionine-bound Se in tissues.
5. The high content of polyunsaturated fatty acids in selenium-rich fish species increases oxidant stress, thereby compromis-

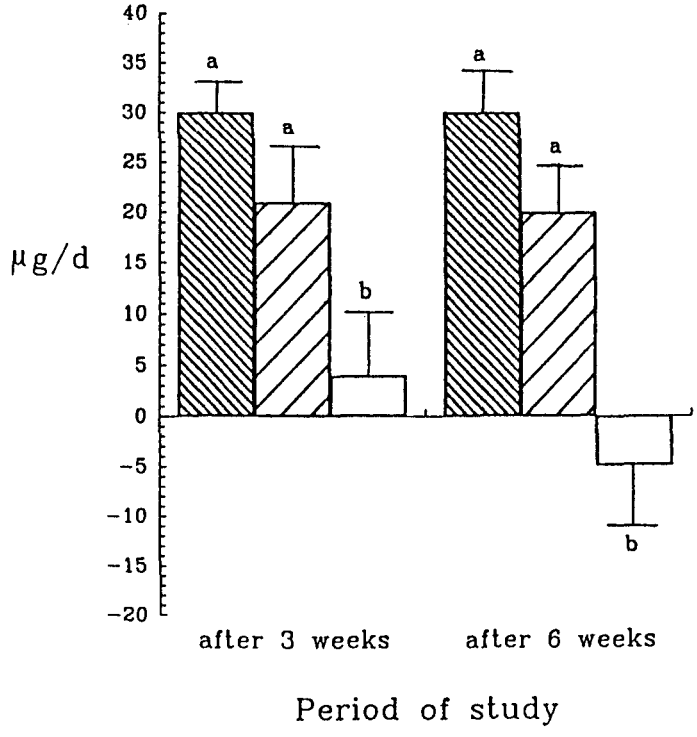

Fig. 3. Changes in urinary selenium levels in the three groups studied: the wheat group (▨), fish group (▨), and control group (□). Points represent means with their standard errors represented by vertical bars. Points at any given action week with different lowercase letters were significantly different ($P < 0.05$; Duncan's multiple-range test). For details of dietary treatments, *see* p. 232.

ing selenium status by increasing the turnover of selenium through glutathione peroxidase.

Further studies will be necessary to clarify all the implied problems satisfactorily, especially explanation 3, but from the present study, some partial answers can be provided:

1. Since approx 55% of the daily selenium intake is recovered in the urine and the absorption of both wheat and fish selenium was adequate, the differences in response may not be explained at this level.
2. The Hg intake of the fish group in this study was 18 ± 5 µg/d compared with 2 and 3 µg/d in the other groups (Table 2). This implies a molar ratio of Se:Hg of 20:1, which makes it probable that some interaction takes place, but that the over-

all bioavailability of fish Se was only marginally influenced by Hg in this study. From animal studies, the interactions between As and Se are well documented, although complicated (*17,29–33*). Depending on dosage, chemical form, and mode and duration of application, As can act both as an antagonist and synergist of selenium toxicity. Marine animals are known to contain As mainly as arsenobetain, which is pharmacologically inert and practically nontoxic (*34,35*). The average daily intake of 806 ± 405 μg As in the fish group is thus unlikely to have influenced the uptake and metabolism of fish Se. Although the As intake varied considerably within this group, there was no correlation between As intake and the changes in platelet Se ($r = -416$, $P = 0.03$, $n = 32$). Therefore, our data do not give any indications of interactions between the As and Se from fish, even if they do not rule out the possibility of such interactions.

3. Little is known about the forms of selenium occurring in fish. From preliminary observations, Ganther (*36*) suggested that a selenonium compound could exist in tuna. As a detoxification product, trimethylselenonium is a poorly available form of Se (*37*). Another substantial part of the selenium in fish could occur in seleno—sulfur bonds (S—Se—S, R—S—SE—R, R—S—Se—S—R) (*38*). In this oxidation state, Se may be prevented from "efficient" incorporation, since it may pass directly into the selenite-exchangeable pool (*39*), which is already "full" at the actual body concentrations of Se. When fish Se does not cause "overflow" of this pool, it may be able to increase serum Se levels, as demonstrated in Se-deplete populations (*40,41*). At the present state of knowledge, this explanation seems to be the most important, if not the only one.
4. The authors did not have the opportunity to measure the methionine content of the diets in this study. However, calculations indicate only modest differences among the groups, the fish group having a somewhat higher intake owing to an increased protein intake.
5. The fish diet contained three times as much marine fatty acids as the others. A large part of these are easily oxidized, and the increased oxidant stress might increase the turnover of GSH-Px, thereby lowering blood Se values. In several studies, it has been observed that the level of vitamin E in serum is lowered in humans taking capsules containing marine fatty acids (*42,43*). Although the explanation seems plausible, multiple-regression analyses of food intake data did not indicate any such effects in the fish group. This matter therefore has to be studied further.

The rise in serum and platelet Se in the wheat group is consistent with earlier findings (*44,45*), where a linear dose–response relationship between wheat Se intake and serum Se was observed. This effect may also partially explain the results of Swanson et al. (*11*), who found a significant correlation between Se intake/kg body wt and serum levels in adult residents of high-Se areas (average intake 174 μg/d, range 68–444) in South Dakota and Wyoming ($n = 44$, $r = 0.63$, $P < 0.01$). Thus, when dietary Se is provided largely by seleno-methionine-rich foods, even relatively Se-replete populations will respond. This is also consistent with the compartment model (*41*), according to which a large part of body Se is in the nonselenite-exchangeable pool and mainly originating from dietary seleno-methionine.

In this and a previous study (*44*), platelet Se has been measured and found to be a good indicator of wheat Se intake at moderate levels. As compared with serum Se, it has proven to be a more sensitive indicator of changes in wheat Se intake, but it remains to be seen whether platelet Se is as sensitive an indicator at low-Se intakes and body values as it has proven to be at moderate to high intakes.

It may be concluded that even if the exact reason is not quite clear, dietary Se from fish contributes only marginally to serum and platelet Se levels in a relatively replete population. Wheat Se, on the other hand, has consistently raised body stores in all our experiments and seems, at present, to be the most important single factor determining the Se status of Norwegians.

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