Bioavailability of selenium to residents in a low-selenium area of China

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ABSTRACT For 8 wk 5 groups of 10 men each were given 0.5 g/day DL-methionine, 150 µg Se/day as sodium selenite with or without methionine or 150 µg Se/day as selenomethionine with or without methionine. Twenty subjects received placebo as controls. Initially plasma Se rose more rapidly than RBC Se. Increases in Se levels were significantly greater with selenomethionine than with the selenite supplement. In the placebo and methionine supplemented groups neither plasma nor RBC Se varied significantly over the course of the study. Supplementation with selenium resulted in marked increases in plasma and RBC GSH-Px within 2 and 4 wk, respectively. Plasma and RBC GSH-Px activity did not differ significantly between Se-supplemented groups. These studies suggest that selenomethionine-Se was more effective in raising plasma and RBC Se than was selenite-Se. Methionine supplements may increase the bioavailability of selenium in severely deficient subjects. Am J Clin Nutr 1985;42:439-448.

KEY WORDS Selenium, bioavailability, selenium status in China, selenium-dependent glutathione peroxidase

Introduction

The nutritional essentiality of selenium in humans was established in 1979 when beneficial responses to Se supplementation were observed in certain patients living in low-Se areas of New Zealand and the People's Republic of China. Chinese scientists reported a dramatic reduction in the incidence of Keshan disease—an endemic cardiomyopathy—after an intervention trial with sodium selenite (1, 2). The New Zealand work implicating Se in human nutrition concerned a patient with muscle cramps who had been given total parenteral nutrition for 29 days because of complications following abdominal surgery (3). When 100 µg of Se as selenomethionine was added to the daily intravenous feeding solution, all muscular symptoms disappeared within 7 days. Deficiency of Se has since been observed in several patients undergoing long-term total parenteral nutrition (3, 4).

Moreover, there are several epidemiological studies suggesting an increased incidence of colon, mammary and perhaps other forms of cancer associated with low levels of environmental Se (5, 6). Selenium compounds added to the diet or water have now been shown to be effective inhibitors of chemical carcinogenesis in different experimental animals (6, 7). Some scientists suggest that Se may possess cancer-protecting properties in the human (6, 8). Selenium may be involved in the conjugation and detoxification of heavy metals and the resulting lowered body and tissue levels of Se have been proposed as a

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factor in the higher levels of cancer associated with some mining and smelting operations (7).

For a number of years, New Zealand and Finland have been known to have areas with low levels of Se in soils, plants, livestock, and human tissue. However, the levels of Se found in certain areas of China (1, 2) are considerably below those previously reported in either New Zealand or Finland. Thus studies carried out in such low-Se areas may provide more valuable basic data needed to elucidate the human requirement for Se.

Sunde and coworkers reported the biopotency of selenomethionine to be decreased in a diet low in methionine especially when fed at levels near the Se requirement (9). These results suggest that adequate dietary methionine is required for optimal utilization of Se in foodstuffs of plant origin since selenomethionine is presumably a major form of plant Se. Since the difference between beneficial and toxic levels for Se in human beings is small, the Se status in a healthy population and the effectiveness of Se supplements for humans under variable dietary conditions must be cautiously determined prior to any Se supplementation recommendation.

The purposes of this study were to ascertain the Se status in a healthy population in Molimo, a low-Se area in North China and to compare in humans the effectiveness of Se and selenomethionine supplements with and without additional dietary methionine.

Methods

Subjects
Six women and 79 men of naturally low-Se status (red blood cells (RBC) Se less than 110 ng/g Hb and GSH-Px activity less than 16 units/g Hb) volunteered to take part in the present study. They were selected for the experiment based on their low-Se status from a group of 160 adults whose Se status was measured between September 15 and October 28, 1983 in Molimo. Subjects with a history of chronic cardiovascular, pulmonary or Keshan disease were excluded. Subjects with elevated SGPT activity were also excluded as they were possible infective hepatitis patients. Study procedures were approved by the Texas Tech University Committee for Protection of Human Subjects and by the Department of Science and Education, Ministry of Health, People’s Republic of China.

Experimental design

This study had two components.

1) Survey study. The purpose of the survey study was to determine adequate dosage of Se supplementation for the treatment study. The 15 adults who participated in this study were divided into 3 groups of 3 men and 2 women each. Group 1 received a placebo while groups 2 and 3 received 50 or 150 µg Se as Na₂SeO₃ daily. Selenium levels and glutathione peroxidase (GSH-Px) activity in plasma and RBC were measured on days 0, 15 and 30 of the Se supplementation period.

2) Treatment study. This study was designed to ascertain the effect of Se supplements on the Se status of residents in a low-Se area. The 70 men in this study were separated into 6 treatment groups as shown in Table 1. For 8 wk groups of 10 men were given 0.5 g/day DL-methionine (Met), 150 µg Se/day as sodium selenite with or without Met (Na₂SeO₃ + Met, or Na₂SeO₃) or 150 µg Se/day as selenomethionine with or without Met (Semet + Met, or Semet). Twenty subjects received a placebo and served as controls. Initial blood samples and background data were obtained October 29–30, 1983. Supplements were begun November 15, and additional blood samples were taken 2, 4, 6 and 8 wk after supplementation began.

Diet
All subjects ate self-selected diets. They were instructed to take only locally produced food. No liver, kidney, or fish were eaten during the experimental period.

Selenium supplementation
The sodium selenite and Semet supplements were compounded in lactose and starch (Beijing Pharmaceuti-

TABLE 1
Characteristics of treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Sex (M:F)</th>
<th>Wt (kg)</th>
<th>Selenium (ng/g Hb)</th>
<th>GSH-Px (units/g Hb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20</td>
<td>27 ± 2</td>
<td>17/20</td>
<td>60.9 ± 1.7</td>
<td>92.3 ± 5.4</td>
<td>14.7 ± 1.1</td>
</tr>
<tr>
<td>Met</td>
<td>10</td>
<td>26 ± 3</td>
<td>7/10</td>
<td>63.6 ± 1.5</td>
<td>97.3 ± 7.2</td>
<td>12.3 ± 0.5</td>
</tr>
<tr>
<td>Na₂SeO₃</td>
<td>10</td>
<td>28 ± 3</td>
<td>6/10</td>
<td>60.1 ± 2.3</td>
<td>91.6 ± 4.8</td>
<td>14.4 ± 3.4</td>
</tr>
<tr>
<td>Na₂SeO₃ + Met</td>
<td>10</td>
<td>27 ± 3</td>
<td>7/10</td>
<td>57.9 ± 2.9</td>
<td>98.9 ± 6.5</td>
<td>14.8 ± 0.9</td>
</tr>
<tr>
<td>Semet</td>
<td>10</td>
<td>28 ± 1</td>
<td>5/10</td>
<td>60.4 ± 2.1</td>
<td>85.2 ± 8.7</td>
<td>15.3 ± 0.7</td>
</tr>
<tr>
<td>Semet + Met</td>
<td>10</td>
<td>30 ± 4</td>
<td>7/10</td>
<td>58.0 ± 1.9</td>
<td>91.9 ± 6.9</td>
<td>14.6 ± 0.7</td>
</tr>
</tbody>
</table>

* Mean ± SEM.
Bioavailability of Selenium in China

Effect of Se supplement as Na₂SeO₃ on the Se concentration in plasma and RBC of residents in Molimo

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 15</th>
<th>Day 30</th>
<th>Day 0</th>
<th>Day 15</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma Se</td>
<td></td>
<td></td>
<td>RBC Se</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>27.0 ± 1.6</td>
<td>27.8 ± 1.7</td>
<td>27.3 ± 3.6</td>
<td>87.0 ± 4.0</td>
<td>86.3 ± 1.7</td>
<td>86.8 ± 6.6</td>
</tr>
<tr>
<td>50 µg/day</td>
<td>29.1 ± 3.9</td>
<td>37.8 ± 4.4</td>
<td>41.4 ± 6.0</td>
<td>91.8 ± 7.0</td>
<td>89.8 ± 6.0</td>
<td>105.7 ± 8.6</td>
</tr>
<tr>
<td>150 µg/day</td>
<td>29.1 ± 4.1</td>
<td>47.2 ± 1.7</td>
<td>59.9 ± 4.0</td>
<td>84.6 ± 7.1</td>
<td>96.8 ± 13.1</td>
<td>122.8 ± 8.7</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
TABLE 3
Effect of Se supplement as Na$_2$SeO$_3$ on the activity of glutathione peroxidase (GSH-Px) in plasma and RBC of residents in Molimo

<table>
<thead>
<tr>
<th>Se supplement</th>
<th>Plasma GSH-Px</th>
<th>RBC GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Day 0</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td>0.054 ± 0.005</td>
</tr>
<tr>
<td>50 µg/day</td>
<td>5</td>
<td>0.053 ± 0.010</td>
</tr>
<tr>
<td>150 µg/day</td>
<td>5</td>
<td>0.054 ± 0.005</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

After 2 wk of supplementation, erythrocyte Se began to rise and appeared to plateau for all Se-supplemented groups after 6 wk. Methionine supplementation exhibited no evident effects in increasing plasma and erythrocyte Se levels in groups given Na$_2$SeO$_3$ or Semaet. Methionine supplementation, however, appeared to delay the plateauing of plasma Se level for groups given Semaet or Na$_2$SeO$_3$ and seemed to slow down the incorporation of supplemented selenite-Se into erythrocytes. Plasma and erythrocyte Se levels in the placebo and methionine groups remained quite steady throughout the intervention period.

Once Se supplementation began, GSH-Px activities in plasma increased promptly for all Se-supplemented groups, GSH-Px activity doubled or tripled in 2 wk and approached a plateau at wk 6 for groups given Semaet and Na$_2$SeO$_3$ plus Met (Fig 3). On the other hand, enzyme activities of groups given Na$_2$SeO$_3$ and Semaet plus Met apparently were still increasing at wk 8.

Supplementation with Se resulted in substantial increases in erythrocyte GSH-Px activities for all Se-supplemented groups at wk 4 (Fig 4). Enzyme activities were similar in all four groups and continued to rise during wk 8. With methionine supplementation, significant increases compared to initial levels were observed in plasma GSH-Px activity at 2, 4, 6 and 8 wk (p < 0.05). GSH-Px activity in RBC increased with the Met supplementation at 4, 6 and 8 wk (p < 0.01). However, the levels of plasma and RBC GSH-Px attained at the end of 8 wk with Met supplementation alone were much lower than with Se supplementation. GSH-Px activities in plasma and RBC of the placebo group remained constant throughout the dosing period.

The paired correlations between Se level and GSH-Px activity in plasma were significant either before (r = 0.44 for 100 samples, p < 0.001) or during the dosing period (r = 0.245 for 76 samples, p < 0.025). Such relationships were not found between Se levels and GSH-Px activities in erythrocytes before Se supplementation; but positive correlations were observed in groups given selenite-Se or Semaet (r = 0.45, n = 78, p < 0.0005, and r = 0.75, n = 74, p < 0.0005, respectively). The regression line for Semaet is shown in Figure 5.

Discussion

The high dose of Se used in this intervention trial was 150 µg/day which is 50 µg below the upper limit of the estimated safe and adequate range for adults established by the US National Research Council (14). Since the mean daily Se intake for residents of Molimo ranged from only 5-13 µg (15) the level of Se supplementation was considered safe for this short-term study of adult male subjects with low-Se status. For men the minimum daily Met intake is estimated to be 1.10 g and the safe daily intake is estimated at 2.20 g (16). The average daily intakes of
FIG 1. Effect of Se supplementation on plasma Se concentration of men with low Se status in Molimo, PRC. Daily supplements of 150 \( \mu g \) Se were started at wk 0 for a period of 8 wk. Supplements were placebo (O - - - O), 0.5 g/d dl-methionine (O - - - O), \( \text{Na}_2\text{SeO}_3 \) (\( \Delta \) -- \( \Delta \)) , \( \text{Na}_2\text{SeO}_3 \) + 0.5 g/d dl-methionine (\( \Delta \) -- \( \Delta \)), Selenomethionine (O ----- O), or Selenomethionine + 0.5 g/d dl-methionine (O ----- O). Each point represents the mean of 8 to 20 subjects. Points at any given wk with different letters are significantly different \((p < 0.05)\) using Duncan’s multiple range test.

Met for adult men in Molimo ranged from 1.06 to 1.85 g, so for this trial the amount of daily Met supplementation was limited to 0.5 g.

The data indicated that Se level and GSH-Px activity increased promptly and significantly in plasma when men of low-Se status were supplemented with \( \text{Na}_2\text{SeO}_3 \) or Semet. There was a 2-wk delay in the RBC GSH-Px response and a somewhat longer delay in some groups before the RBC Se levels became significantly higher than controls. Our data agree closely with those reported by Steiner et al (17). They observed a significant increase in plasma GSH-Px activity in severely deficient children who were supplemented with
Se-rich yeast, but this contradicts a more recent study in which Levander et al (18) found only a small increase in plasma GSH-Px activity during Se supplementation to adult Finnish men. It is possible that this discrepancy might be related to the extremely low-Se status of our subjects as compared to the moderately low-Se status in their study.

Since Semet has been identified as a major form of Se present in cereals (19, 20), it deserves special comment. Our data showed that Semet was more effective in raising plasma and RBC Se than was Na$_2$SeO$_3$, but the mean increases in GSH-Px activities for the two forms were not significantly different. Thomson et al (21) and Robinson et al (22) likewise showed that increases in Se concentration in whole blood, erythrocytes, and plasma were greater after Semet than after Na$_2$SeO$_3$. Selenium from ($^{75}$Se)-selenomethionine was also reported to be more completely absorbed by humans than Se from ($^{75}$Se)-selenite (23, 24).

Supplementation with Semet compared to Na$_2$SeO$_3$ produced higher circulating Se levels but not greater GSH-Px activity in plasma.
and erythrocytes. Possible explanations include: 1) plasma and erythrocyte Se may reflect circulating Semet from the supplement that has not been incorporated into GSH-Px; or 2) Semet may be better absorbed but other factors may prevent Se incorporation into GSH-Px. A dose smaller than 150 μg of Se/day may be required to actually test the bioavailability of selenomethionine vs Na₂SeO₃ in this population. With 150 μg Se, GSH-Px levels in plasma and RBC increased sharply between 2 and 4 wk and the groups were indistinguishable.

Sunde and coworkers (9) reported that in rats Semet was more extensively incorporated into protein when dietary methionine was suboptimal making less Se available for GSH-Px synthesis. In our studies a similar decrease in biopotency of Semet was not observed in groups given Semet without Met supplements.
It is likely that with 150 μg Se supplements compared to controls. Beilstein and Whanger noted that a significant amount of GSH-Px activity in a human erythrocyte lysate co-chromatographed with hemoglobin rather than with Se-dependent GSH-Px (25). In our study, the GSH-Px activity was not chromatographed, so it was not possible to determine whether the methionine supplements alone increased the Se-dependent or non-Se-dependent GSH-Px activity. A more likely explanation for the increased RBC GSH-Px
activity may be that with added methionine there is less incorporation of Semet-Se from food into protein, leaving more Se available for GSH-Px synthesis (9).

In subjects given Met supplements, plasma Se level appeared to plateau more slowly for groups given either Semet or Na₂SeO₃. An explanation for these results will require further study.

Our studies performed thus far suggest that:

1) Daily supplementation with 150 μg Se for more than 2 mo may be needed by residents in a low-Se area, like Molimo, to increase plasma and RBC Se and GSH-Px activity to the levels of people in a Se-adequate area (Beijing).

2) Supplementation with Semet compared to Na₂SeO₃ produced higher circulating Se levels but not greater GSH-Px activity in plasma and erythrocytes.

3) In subjects receiving no Se supplements, RBC GSH-Px increased significantly with Met supplements. A column separation of the GSH-Px from the RBC lysate would be necessary to determine whether the Met effect is on Se-dependent GSH-Px or on non-Se-dependent GSH-Px activity. No long-term significant effects of Met were seen in groups supplemented with either Na₂SeO₃ and Semet.

4) Selenium concentration and GSH-Px activities in plasma and erythrocytes were confirmed as sensitive indices of changes in Se status in people from an extremely low-Se area. Plasma Se concentrations and GSH-

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**FIG 5. Regression of glutathione peroxidase activity vs Se concentration of erythrocytes in men with low Se status supplemented with selenomethionine in Molimo, PRC.**
Fx activities were readily influenced by changes in Se intake.

References
