Bioavailability of selenium to residents in a low-selenium area of China[1-3]

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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 Na_2SeO_3 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 (Na_2SeO_3 + Met, or Na_2SeO_3) 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.

Diets

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 Pharmaceu-

TABLE 1
Characteristics of treatment groups*

Group	n	Age	Smokers	Wt	Prestudy RBC	
					Selenium	GSH-Px
		yr		kg	ng/g Hb	units/g Hb
Placebo	20	27 ± 2	17/20	60.9 ± 1.7	92.3 ± 5.4	14.7 ± 1.1
Met	10	26 ± 3	7/10	63.6 ± 1.5	97.3 ± 7.2	12.3 ± 0.5
Na_2SeO_3	10	28 ± 3	6/10	60.1 ± 2.3	91.6 ± 4.8	14.4 ± 3.4
Na_2SeO_3 + Met	10	27 ± 3	7/10	57.9 ± 2.9	98.9 ± 6.5	14.8 ± 0.9
Semet	10	28 ± 1	5/10	60.4 ± 2.1	85.2 ± 8.7	15.3 ± 0.7
Semet + Met	10	30 ± 4	7/10	58.0 ± 1.9	91.9 ± 6.9	14.6 ± 0.7

* Mean ± SEM.

ticals, Beijing, PRC). Placebo tablets contained only these two items and were not distinguishable from Se supplements. Chemical analysis showed that the placebo products contributed negligible quantities of Se to the total daily intake. Six local cadres who were especially trained took charge of the daily supplements. The subjects were instructed to take the placebo or supplements in the morning.

DL-Methionine supplementation

The amount of daily Met supplementation was 0.5 g. The DL-methionine used in this study contained 0.00263 ppm Se and thus provided only 0.0013 μg of Se a day to the methionine-supplemented subjects. Plasma and RBC Se level remained quite steady over the Met supplement period.

Blood sample preparation and analyses

Fasting blood samples were drawn by venipuncture early in the morning. Hemoglobins were determined on an aliquot of whole blood. Six ml of blood was treated with 0.1 ml of 10.0% potassium oxalate and centrifuged. Plasma was then removed and frozen. The RBC were maintained in 2.0 ml ACD solution (Acid-Citrate-Dextrose, citric acid 0.540 g, trisodium citrate 1.485 g, dextrose 1.687 g and water to 67.5 ml) at 4°C until analysis for GSH-Px activity (usually finished within 72 h). Sera were prepared from the remaining blood samples for SGPT and protein determination.

Selenium levels were measured from plasma or RBC by a modification (10) of the 2,3-diaminonaphthalene fluorometric method of Watkinson (11). Samples were analyzed in duplicate. Blood cells were washed twice with physiological saline (9 g NaCl/l). Hemolysates for enzyme assays were prepared by adding 0.1 ml of washed RBC to 0.9 ml deionized water. To this hemolysate an equal volume of double strength Drabkin's reagent (0.016 M KCN, 0.0012 M $K_3Fe(CN)_6$, 0.238 M $NaHCO_3$) was added. A fraction was again diluted with 20 mM phosphate buffer (pH 7.0) for GSH-Px activity analysis. GSH-Px activities were assayed by a modification of the coupled method of Paglia and Valentine (12) using hydrogen peroxide as substrate. The reaction mixture had the following composition: 20 mM phosphate buffer (pH 7.0) 15.0 ml, 10 mM sodium azide 2.0 ml; NADPH 3.0 mg; glutathione 12.3 mg and glutathione reductase 0.1 ml (20 units). Hemolysate or plasma (50 μl) was added to 0.6 ml of the mixture and incubated for 10 min at 25°C after which the reaction was initiated by adding 50 μl of 5 mM H_2O_2 (the concentration of H_2O_2 was estimated by an iodometric method on the day of assay) and analyzed immediately. Absorbance at 340 nm was recorded. The reaction was followed for 2–4 min. The nonenzymic rate of NADPH oxidation was subtracted from each assay. One unit of activity was defined as 1 μmol NADPH oxidized/min and the results expressed as units/ml plasma or units/g Hb for RBC.

Chemical reagents

Selenomethionine, DL-methionine, NADPH, glutathione, glutathione reductase, sodium azide, and KCN were purchased from Sigma Chemical Co St Louis, MO. The remaining reagents were from Beijing Chemical Reagent Co, Beijing, PRC.

Statistical analysis

The experimental data were subjected to one-way analysis of variance and compared by Duncan's multiple range test (13).

Results

Survey study

All measured Se and GSH-Px values for Group 1 (placebo) remained quite constant over the course of the study (**Tables 2 and 3**). After 30 days supplementation, Se levels and GSH-Px activities of plasma and RBC increased moderately in Group 2. In Group 3, plasma Se and GSH-Px activity and RBC Se and GSH-Px activities reached 59.9 ng/ml and 0.127 units/ml or 122.8 ng/g Hb and 14.8 units/g Hb, respectively. These values were still much lower than those (93.4 ng/ml and 0.126 units/ml or 262.8 ng/g Hb and 22.0 units/g Hb) of residents of Beijing, a Se-adequate area. The data suggest that a supplement of more than 50 μg Se daily for 30 days may be needed by people in a low-Se area like Molimo to increase Se and GSH-Px to levels found in residents of Beijing.

Treatment study

Plasma and RBC Se levels at wk 0 did not differ significantly among the six treatment

TABLE 2
Effect of Se supplement as Na_2SeO_3 on the Se concentration in plasma and RBC of residents in Molimo*

Group	n	Plasma Se			RBC Se		
		Day 0	Day 15	Day 30	Day 0	Day 15	Day 30
		ng/ml			ng/g Hb		
Placebo	5	27.0 ± 1.6	27.8 ± 1.7	27.3 ± 3.6	87.0 ± 4.0	86.3 ± 1.7	86.8 ± 6.6
50 μg/day	5	29.1 ± 3.9	37.8 ± 4.4	41.4 ± 6.0	91.8 ± 7.0	89.8 ± 6.0	105.7 ± 8.6
150 μg/day	5	29.1 ± 4.1	47.2 ± 1.7	59.9 ± 4.0	84.6 ± 7.1	96.8 ± 13.1	122.8 ± 8.7

* Mean ± SEM.

TABLE 3
Effect of Se supplement as Na_2SeO_3 on the activity of glutathione peroxidase (GSH-Px) in plasma and RBC of residents in Molimo*

Se supplement	n	Plasma GSH-Px			RBC GSH-Px		
		Day 0	Day 15	Day 30	Day 0	Day 15	Day 30
		units/ml			units/g Hb		
Placebo	5	0.054 ± 0.005	0.048 ± 0.006	0.054 ± 0.002	13.0 ± 1.7	13.5 ± 1.6	13.1 ± 1.5
50 μg/day	5	0.053 ± 0.010	0.071 ± 0.008	0.088 ± 0.007	13.5 ± 1.9	13.2 ± 0.8	14.0 ± 0.9
150 μg/day	5	0.054 ± 0.005	0.098 ± 0.007	0.127 ± 0.016	11.3 ± 1.0	13.1 ± 0.4	14.8 ± 1.0

* Mean ± SEM.

groups (**Figs 1 and 2**). Plasma Se initially rose more rapidly than erythrocyte Se and differences between the groups became obvious after only 2 wk (Fig 1). After 8 wk increases in both plasma and erythrocyte Se were greater after Semet than after Na_2SeO_3 with or without Met supplements. Plasma Se reached a plateau with Na_2SeO_3 supplementation at wk 4 and with Na_2SeO_3 plus Met and Semet, at wk 6. With supplements of Semet plus Met, plasma Se continued to rise with no sign of plateauing at wk 8.

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_2SeO_3 or Semet. Methionine supplementation, however, appeared to delay the plateauing of plasma Se level for groups given Semet or Na_2SeO_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 Semet and Na_2SeO_3 plus Met (**Fig 3**). On the other hand, enzyme activities of groups given Na_2SeO_3 and Semet 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 or Semet ($r = 0.45$, $n = 78$, $p < 0.0005$, and $r = 0.75$, $n = 74$, $p < 0.0005$, respectively). The regression line for Semet 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

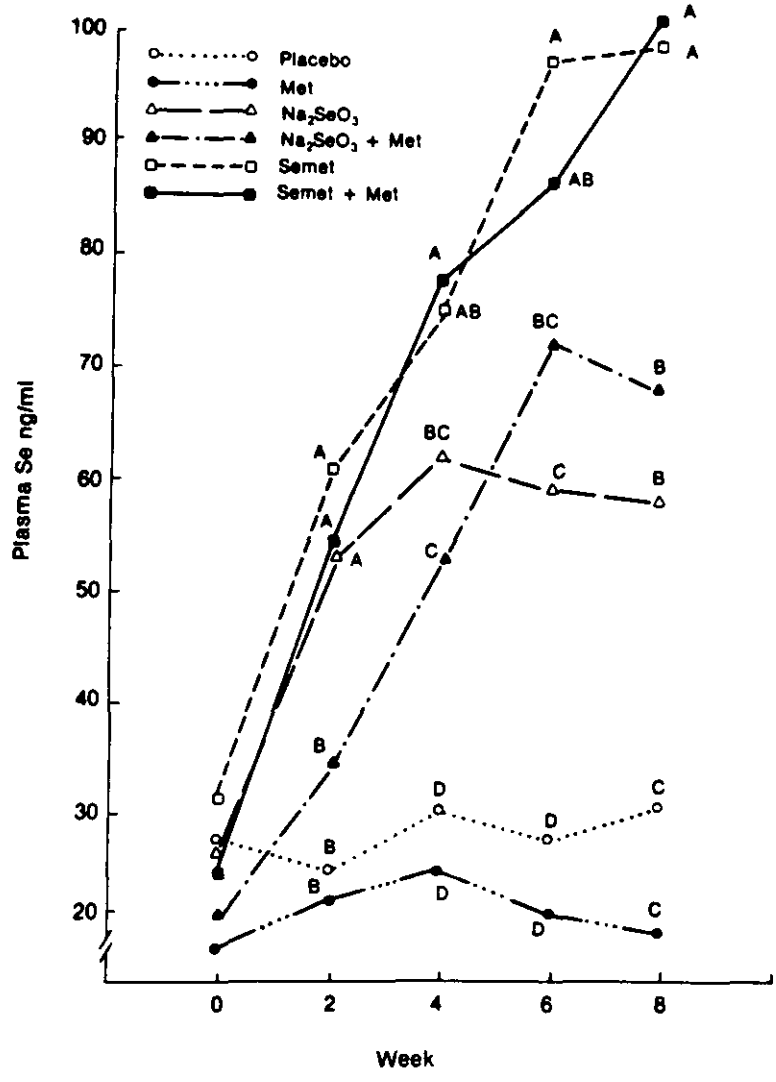

FIG 1. Effect of Se supplementation on plasma Se concentration of men with low Se status in Molimo, PRC. Daily supplements of 150 μg Se were started at wk 0 for a period of 8 wk. Supplements were placebo (O · · · O), 0.5 g/d DL-methionine (● – · · · – ●), Na_2SeO_3 (Δ – – – Δ), Na_2SeO_3 + 0.5 g/d DL-methionine (▲ – · – · – ▲), Selenomethionine (□ ----- □), or Selenomethionine + 0.5 g/d DL-methionine (■ —— ■). 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 Na_2SeO_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

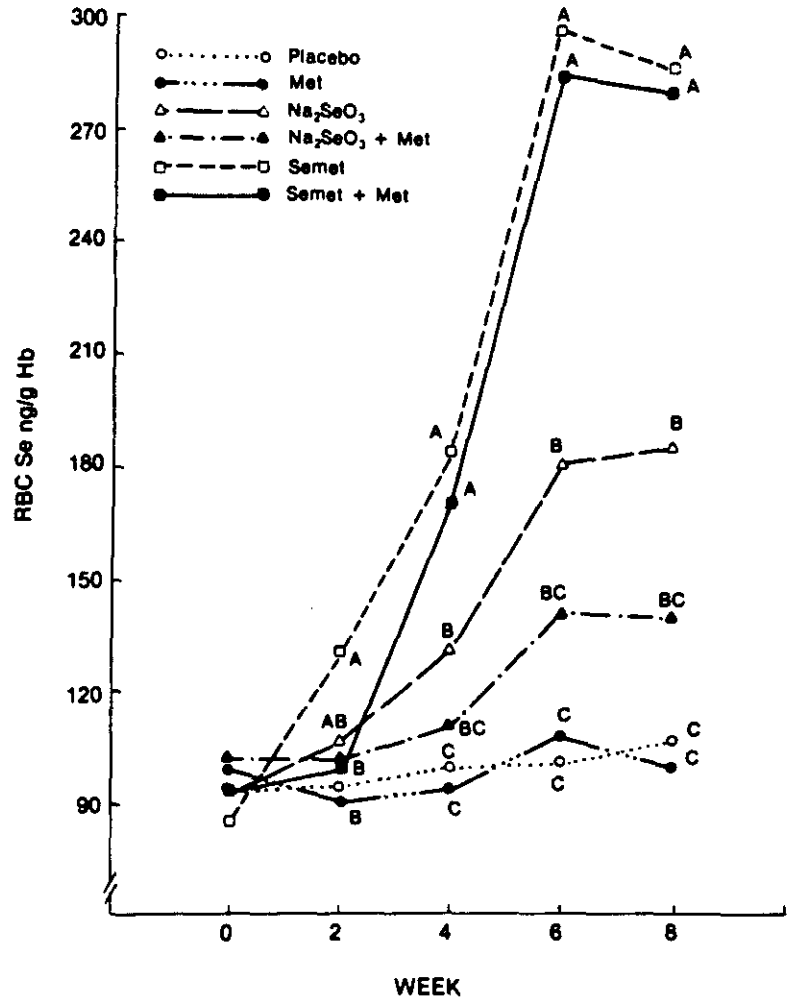

FIG 2. Effect of Se supplementation on erythrocyte Se level of men with low Se status in Molimo, PRC. See Figure 1 for explanation.

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_2SeO_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_2SeO_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_2SeO_3 produced higher circulating Se levels but not greater GSH-Px activity in plasma

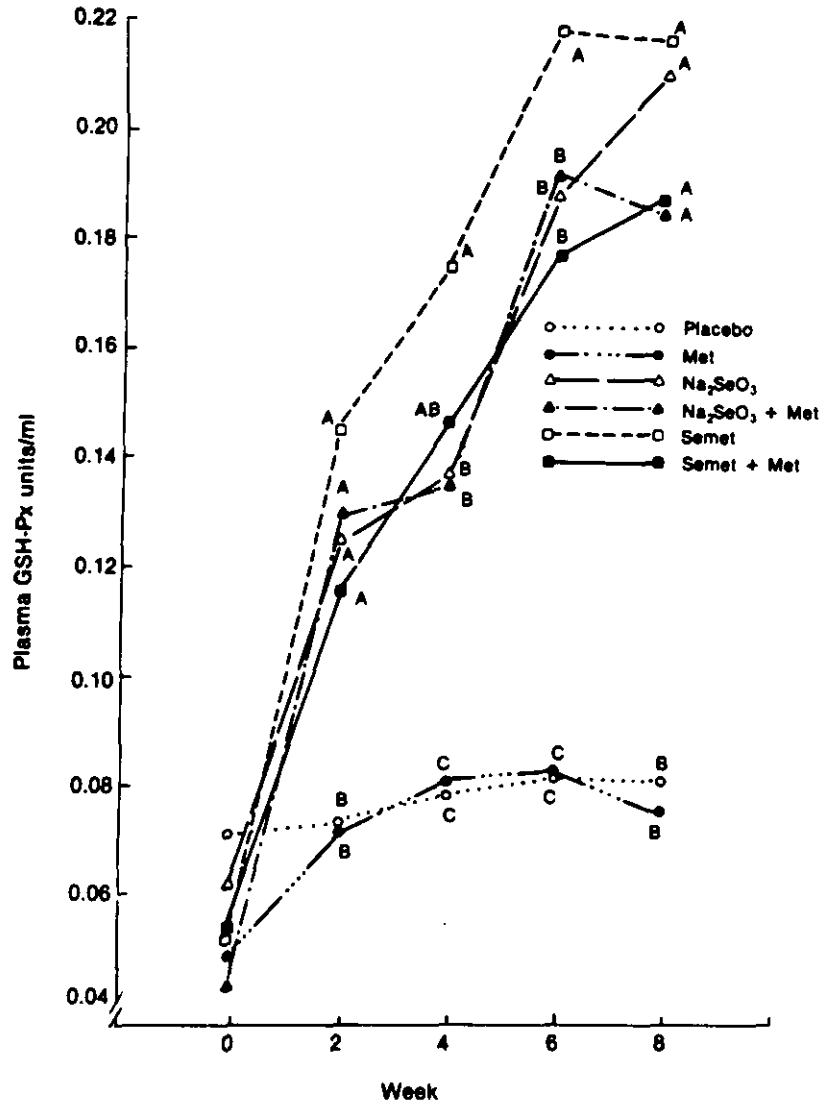

FIG 3. Effect of Se supplementation on plasma glutathione-peroxidase activity in men with low Se status in Molimo, PRC. See Figure 1 for explanation.

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 Na_2SeO_3 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.

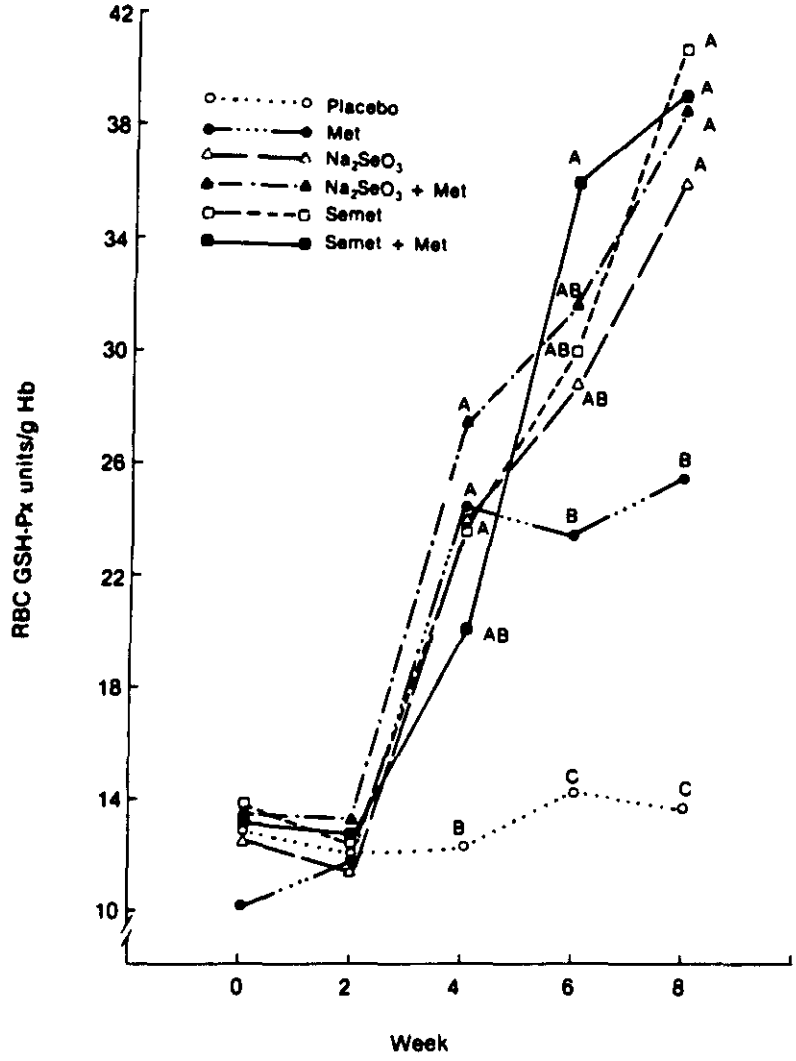

FIG 4. Effect of Se supplementation on erythrocyte glutathione-peroxidase activity in men with low Se status in Molimo, PRC. See Figure 1 for explanation.

It is likely that with 150 μg Se supplements the daily Met intakes of residents were not low enough to reduce bioavailability of Se from selenomethionine to an extent detectable using plasma GSH-Px.

Results based on the RBC GSH-Px assay likewise showed no evident effects of Met supplements on the bioavailability of Se from either Semet or Na_2SeO_3 supplements. However, RBC GSH-Px activity of the group supplemented only with methionine increased 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

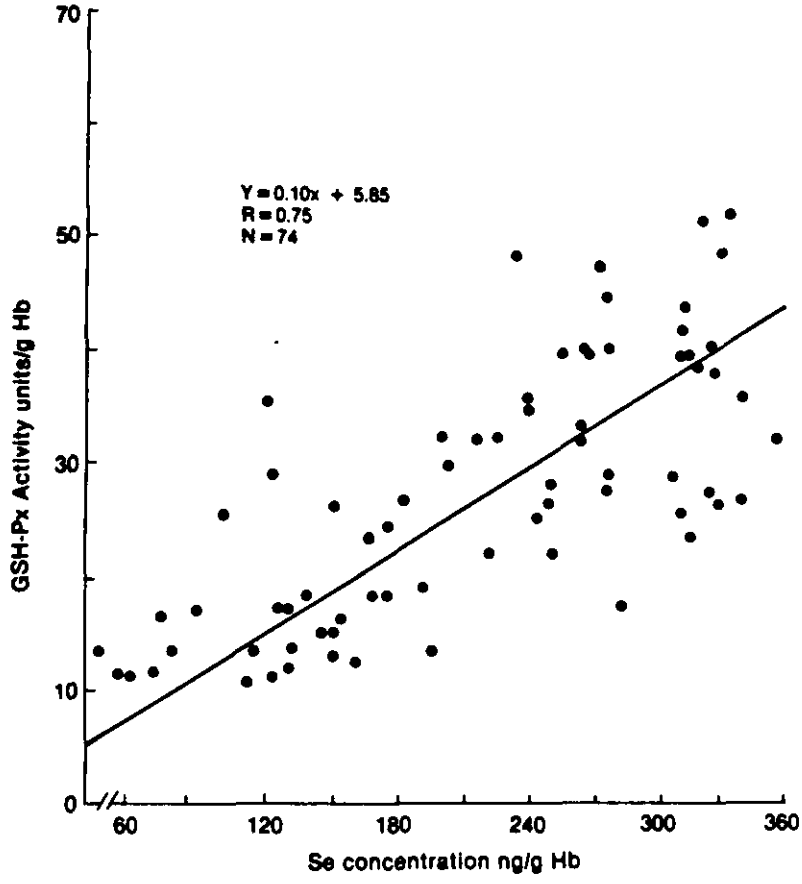

FIG 5. Regression of glutathione peroxidase activity vs Se concentration of erythrocytes in men with low Se status supplemented with selenomethionine in Molimo, PRC.

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 Na_2SeO_3. 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 Na_2SeO_3 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 Na_2SeO_3 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-

Px activities were readily influenced by changes in Se intake.

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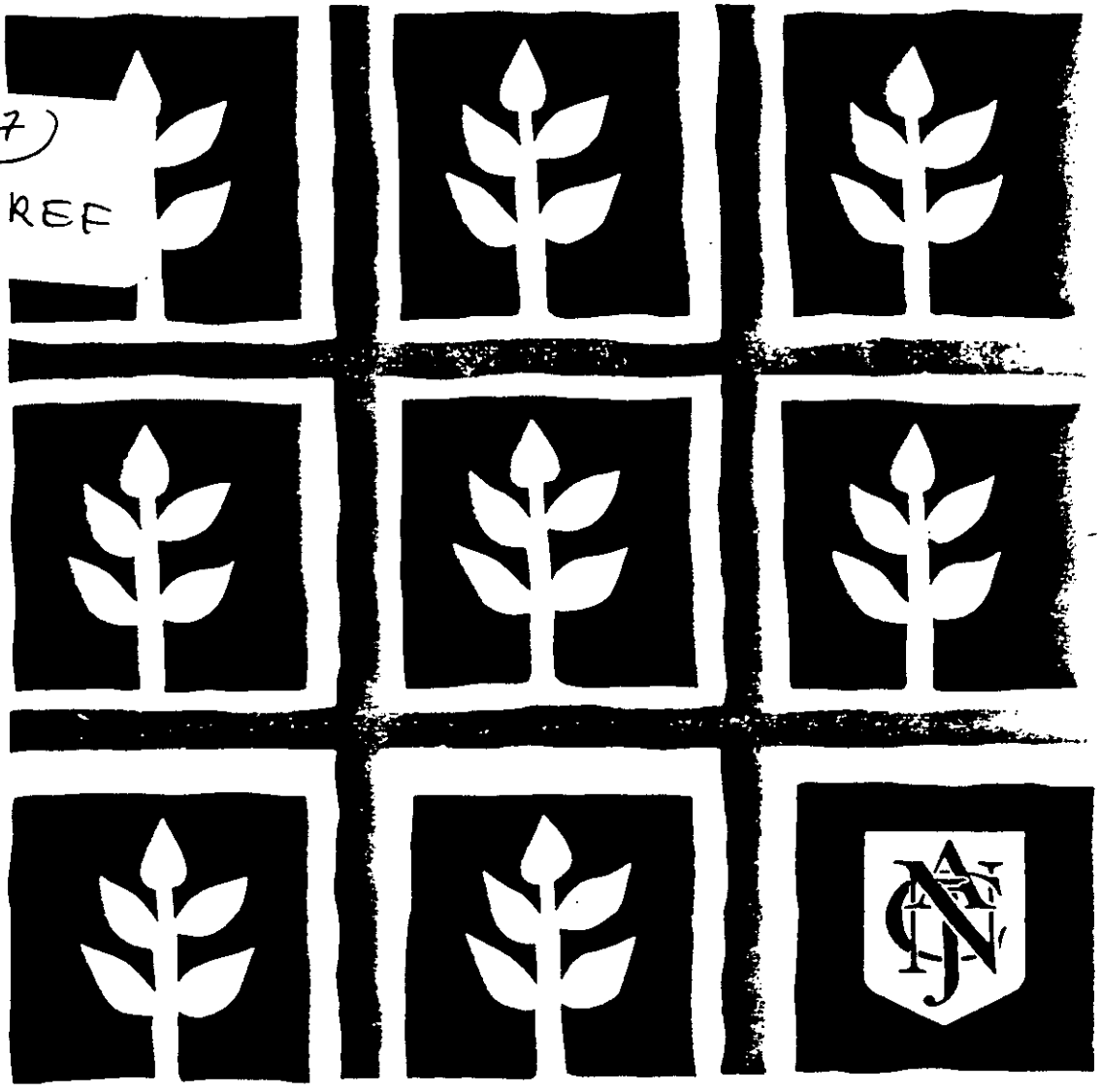

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