Selenium and iodine supplementation of rural Tibetan children affected by Kashin-Beck osteoarthropathy[1–3]

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ABSTRACT

Background: Kashin-Beck disease is an osteoarthropathy endemic in selenium- and iodine-deficient areas around Lhasa, Tibet.

Objective: We assessed the efficacy of selenium supplementation on disease progression.

Design: A double-blind, randomized controlled trial of selenium supplementation was carried out in 324 children aged 5–15 y who had Kashin-Beck disease. Two hundred eighty children received iodized oil before being randomly assigned to receive selenium or placebo, and a control group of 44 subjects was not supplemented at all. Clinical and radiologic signs, selenium status, urinary iodine, and thyroid function were evaluated at baseline and at 12 mo.

Results: The frequencies of joint pain, decreased joint mobility, and radiologic abnormalities were not significantly different between the 3 groups at 12 mo. Height-for-age *z* scores increased significantly in the subjects who received placebo and iodine or selenium and iodine. In contrast, unsupplemented control subjects did not recover from growth retardation. Serum selenium concentrations at 12 mo were within the reference range and were significantly greater in the selenium-iodine group than in the placebo-iodine group. Serum thyroid hormone concentrations were within the reference ranges after the administration of iodine, and these values were not significantly affected by selenium supplementation.

Conclusions: The results of this study do not rule out the possibility that selenium may help to prevent the occurrence of Kashin-Beck disease. However, selenium supplementation had no effect on established Kashin-Beck disease, growth, or thyroid function once iodine deficiency was corrected. These results suggest that iodine, but not selenium, deficiency should be corrected in Tibetan children with Kashin-Beck disease. *Am J Clin Nutr* 2003;78:137–44.

KEY WORDS Selenium, iodine, Kashin-Beck disease, osteoarthropathy, Tibet

INTRODUCTION

Kashin-Beck disease is an osteoarthropathy endemic in certain areas of China, Siberia, and North Korea that causes joint deformation and limited joint mobility (1, 2). The most severe cases of the disease result in decreased limb length and short stature. Selenium deficiency has been suggested as a risk factor because the disease is limited to low-selenium areas (3, 4). However, the efficacy of selenium in the prevention of Kashin-Beck disease is controversial (4). In a cross-sectional community survey in Tibet, we found no association between individual selenium status and Kashin-Beck disease, whereas iodine deficiency was a risk factor (5). Although the Tibetan health authorities recommend iodization of salt, there is evidence that this recommendation is rarely put into practice in remote communities. In our baseline study, we found extremely low urinary iodine concentrations in almost all the study subjects, ie, children with or without Kashin-Beck disease (5). Other risk factors for Kashin-Beck disease, such as fungal contamination, have also been suggested (6). Tibetan health authorities have advocated selenium supplementation, but the supplementation program is not strictly adhered to. When Médecins sans Frontières started a health program in the area in 1992, there was little scientific evidence to support large-scale preventive selenium supplementation. Because the huge numbers of Kashin-Beck cases were of more immediate concern, Médecins sans Frontières decided to launch a physiotherapy program. In addition, the hypothesis was raised that if selenium deficiency was supposedly a contributing factor to the onset of the disease, selenium supplementation might possibly reduce the osteoarticular damage or correct growth retardation in persons with the disease. In this double-blind, randomized controlled trial, we evaluated the effect of 12 mo of selenium supplementation in combination with iodine on clinical symptoms and signs, thyroid metabolism, and growth in Tibetan subjects with Kashin-Beck disease. Because selenium supplementation in iodine-deficient subjects can aggravate a status of hypothyroidism (7), we first corrected iodine deficiency before randomly assigning study subjects to receive selenium or placebo.

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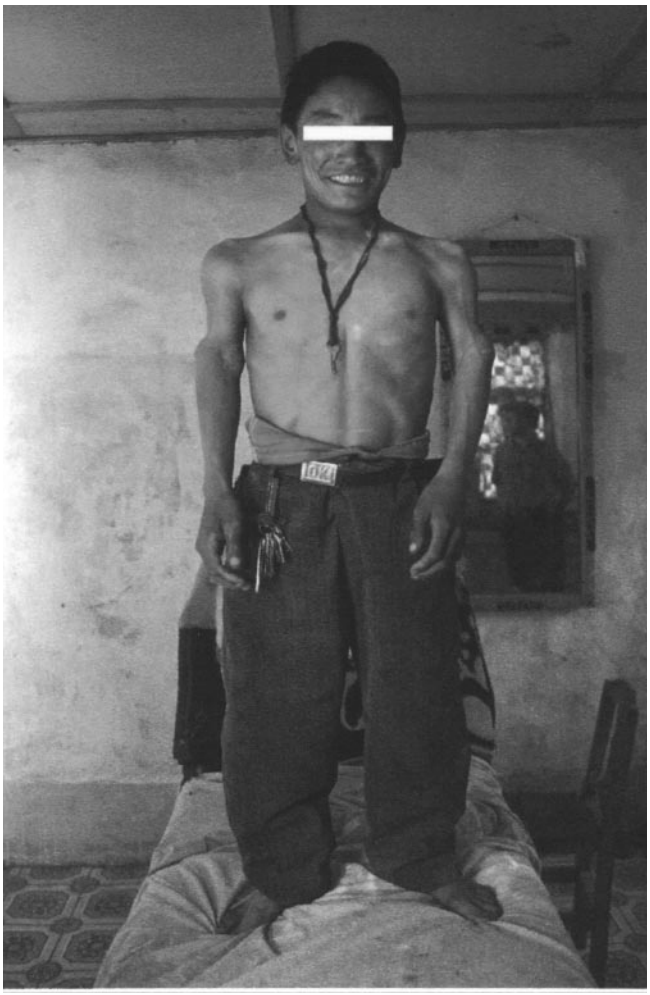

FIGURE 1. Male, 16-y-old Tibetan adolescent with Kashin-Beck disease. The picture shows some of the signs of severe Kashin-Beck disease (stage III), with bilateral shortening and deformation of the distal ends of the humerus. The adolescent (height 1.45 m) was smaller than healthy Tibetan adolescents of the same age, although he was not dwarfed. The hands and joints of the lower limbs were affected.

SUBJECTS AND METHODS

Study subjects

The study area was situated in Lhasa prefecture, Tibet, where 12 villages with known Kashin-Beck disease occurrence were selected. The villages had a median population size of 143 inhabitants (quartile 1: 125; quartile 3: 185). Only subjects aged 5–15 y who were affected by Kashin-Beck disease were eligible for the study. Two members of the study team visited each household in the villages and invited all subjects aged 5–15 y to report to the health center. The age-specific prevalence rate of Kashin-Beck disease for children aged 5–15 y ranged from 13% to 100% (median: 56%) (5). Kashin-Beck disease was diagnosed when a child had persistent pain, restricted mobility, or deformity of the knees, ankles, elbows, wrist, interphalangeal joints, hips, or shoulders, as shown by physical examination, in the absence of local inflammation or history of trauma (8). An intramuscular injection of 1 mL iodized oil (Lipiodol, 475 mg I/mL; Guerbet, Aulnay-sous-bois, France) was given to subjects 4 mo before the selenium supplementation. Subsequently, subjects affected by Kashin-Beck disease were randomly and double-blindly assigned either to placebo (placebo-iodine group) or selenium (selenium-iodine group) supplementation. If several persons with Kashin-Beck disease were found within the same household, they were block-assigned to either the placebo-iodine group or the selenium-iodine group to avoid contamination. A group of 44 children with Kashin-Beck disease was recruited in a separate village to act as a control group. These children were not supplemented with iodine or selenium during the study. The evolution of Kashin-Beck disease and growth patterns were studied in this group to control for any environmental or nutritional trend. All of these children received iodine supplementation at the end of the study period. The study protocol was approved by the Lhasa Health Bureau of Tibet and by the institutional review board of the Ambroise Paré Hospital of Mons, Belgium. Enrollment in the study was conditional on informed consent from the caretaker. The present study was conducted from May 1995 through November 1996.

Intervention

The selenium-iodine group received 100 μg Se/d and 1 mg Se/wk in the form of sodium selenate tablets (Laboratoria Wolfs, Antwerp, Belgium) for 11 mo. The placebo-iodine group received tablets having an appearance identical to that of the selenate tablets but containing no active substance. During the 12th month, both groups received only the weekly 1-mg selenate or placebo tablets because the supply of 100-μg tablets was interrupted as a result of logistical problems.

The dosing schedule described above was an adaptation to the very difficult field conditions in Tibet and was aimed at effective supplementation in the intervention group. Direct supervision by study investigators of daily tablet intake was not possible because most of the study villages were very remote from Lhasa. Therefore, the community health worker of the village was instructed to give a daily dose of 100 μg Se or placebo to the study subjects. The investigators visited the villages once a week and gave a tablet containing 1 mg Se or placebo to each of the study subjects, who ingested it under direct observation.

Clinical examination

All children were interviewed with a standardized questionnaire and examined by a physiotherapist, who was blinded to the study group, at the start and at 12 mo of selenium supplementation. Work ability, joint pain during the past 24 h, and morning joint stiffness were recorded for every subject in the 2 intervention groups. The patients' disease was classified into 3 stages according to the presence of at least one enlarged joint, pain, degree of limitation, and the following associated symptoms: tiredness, muscle weakness, ability to work, flat feet, waddling gait, and dwarfism (**Figure 1**; 8).

The main endpoint of the study, clinical improvement, was defined as an improvement of at least one stage on the scale of clinical severity. A height-for-age, height-for-weight, and weight-for-age index was calculated for each subject on the basis of reference tables from the National Center for Health Statistics, the Centers for Disease Control and Prevention, and the World Health Organization (9).

Laboratory measurements

Blood samples were collected for measurement of serum selenium, glutathione peroxidase activity (GPX), thyroxine, triiodothyronine,

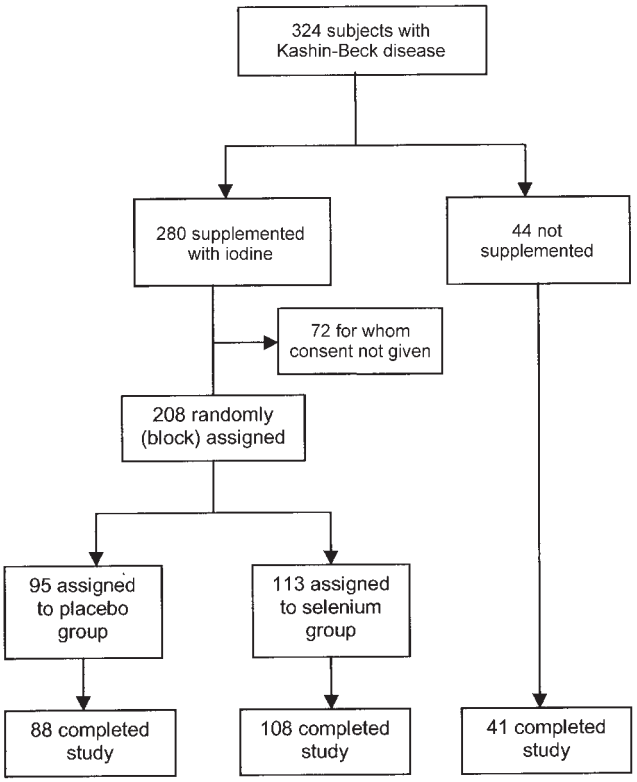

FIGURE 2. Trial profile.

thyrotropin, and thyroxine-binding globulin. Urine samples were collected for measurement of selenium and iodine and to monitor iodine status and compliance with selenium supplementation. Serum selenium was measured by atomic absorption spectrometry with Zeeman background correction (Perkin-Elmer Z3030; Perkin-Elmer, Uberlingen, Germany) (10). GPX was measured spectrophotometrically on a biochemical analyzer (Hitachi 717; Boehringer-Mannheim, Mannheim, Germany) as previously described (5). Serum thyroxine, triiodothyronine, and thyrotropin were measured by chemiluminescence detection (ACS 180; Corning, Los Angeles). Serum thyroxine-binding globulin was measured by radioimmunoassay with commercial kits (Biocode, Liège, Belgium). Urinary iodine was measured by using a Technicon Autoanalyzer (Technicon, Tarrytown, NY) (5). Urine selenium was measured by fluorimetry (luminescence spectrophotometer LS50B; Perkin-Elmer) after reaction with 2,3-diaminonaphthalene (11). The reference ranges for healthy adults in Belgium were as follows: thyroxine, 77–154 nmol/L; triiodothyronine, 1.2–3.0 nmol/L; thyrotropin, 0.3–4.6 mU/L; serum selenium, 60–105 μg/L; GPX, 550–1100 U/L; urinary iodine, 50–250 μg/L; and urinary selenium, 10–50 μg/L.

Radiologic evaluation

Radiographs of the right hand and foot were taken at the start of selenium supplementation and after 12 mo. A pediatric radiologist, who was blinded to the subjects' study group, rated the films. Skeletal maturity was assessed according to Greulich and Pyle (12). Skeletal delay was calculated as chronologic age minus radiologic bone age. A radiologic diagnosis of Kashin-Beck disease was made if the subject had at least one of the following signs: irregular erosion of carpal or tarsal bones, irregular metaphyseal widening, irregular erosions of the metacarpal or metatarsal bones and phalanges, cone-shaped epiphyses of phalanges, fragmentation of the cone-shaped epiphysis, premature closure of the metaphysis with subsequent shortening of the metacarpal or metatarsal bone and phalanges, or talus collapse with bone densification. Radiologic improvement was defined as regression or disappearance of existing lesions by comparing films taken before and after selenium supplementation.

Statistical analysis

For serum thyrotropin, selenium, GPX, and urinary iodine, the geometric mean was computed because the log-transformed values fitted a normal distribution better than the untransformed values did. Differences between independent means were tested by one-factor analysis of variance, and the Scheffe multiple comparison test was used to compare pairs of means. For paired samples, a paired *t* test was used. Differences between proportions were tested by chi-square tests. All *P* values were two sided. A two-factor repeated-measures analysis of variance was performed, with time as the within-factor variable and treatment as the between-factor variable, to compare the effects of time and treatment and time-by-treatment interactions for weight-for-height, weight-for-age, and height-for-age *z* scores; urinary iodine and selenium; and serum thyroxine, triiodothyronine, and thyrotropin. If the interaction was significant, *t* tests between groups were done and adjusted for multiple comparisons (Bonferroni correction). The statistical analyses were performed with SPSS for WINDOWS, release 10.0.5 (SPSS Inc, Chicago).

RESULTS

Subjects and baseline characteristics

Among the 324 subjects with Kashin-Beck disease who were recruited, 280 received iodine. Because the caretakers of 72 subjects did not give consent, only 208 subjects were included in the supplementation trial. Forty-four subjects were not supplemented with selenium or iodized oil (**Figure 2**). The characteristics of the unsupplemented group, the placebo-iodine group, and the selenium-iodine group at baseline, ie, 4 mo after iodine supplementation and before the start of selenium or placebo supplementation, are shown in **Table 1**. Skeletal delays, height-for-age *z* scores, clinical severities, and frequencies of radiologic abnormalities were not significantly different between the 3 groups. The unsupplemented group had significantly lower serum thyroxine concentrations and significantly higher serum triiodothyronine and thyrotropin concentrations than did the iodine-supplemented groups. Serum thyroxine, triiodothyronine, and thyrotropin concentrations were within the reference ranges in the 2 iodine-supplemented groups. The mean urinary iodine concentration in the unsupplemented group was below the reference range (50–250 μg/L), but the mean concentrations in the 2 iodine-supplemented groups were within the reference range. Serum selenium concentrations and serum GPX were very low and did not differ significantly between the 3 groups.

TABLE 1
Baseline characteristics of unsupplemented subjects with Kashin-Beck disease and of iodine-supplemented subjects with Kashin-Beck disease who were assigned to receive placebo or selenium[1]

Characteristic	Unsupplemented	Placebo and iodine	Selenium and iodine	P[2]
Age (y)	10 ± 0.5[3] [44][4]	10 ± 0.3 [95]	10 ± 0.28 [113]	0.79
Sex, male [*n* (%)]	17 (39)	61 (64)	72 (64)	0.008[5]
Weight (kg)	23.9 ± 1.1 [44]	26.8 ± 0.8 [95]	26.6 ± 0.7 [113]	0.10
Height (cm)	119 ± 2.2 [44]	122 ± 1.5 [95]	121 ± 1.4 [113]	0.61
Skeletal delay (y)	2.7 ± 0.3 [41]	2.8 ± 0.1 [93]	2.9 ± 0.1 [104]	0.67
Height-for-age *z* score	−3.1 ± 0.1 [44]	−3.0 ± 0.1 [95]	−3.2 ± 0.1 [113]	0.42
Scale of clinical severity [*n* (%)]				
Stage I	34 (77)	79 (83)	95 (84)	0.84
Stage II or III	10 (23)	16 (17)	18 (16)	0.84
Radiologic abnormalities [*n* (%)]	7 (18)	11 (12)	16 (14)	0.65
Serum T_4 (nmol/L)	81 ± 5 [39]	97 ± 3 [80]	107 ± 3 [92]	<0.001
Serum T_3 (nmol/L)	2.3 ± 0.1 [39]	1.9 ± 0.03 [79]	2.1 ± 0.03 [93]	<0.001
Serum TBG (mg/L)	18.5 ± 0.7 [41]	18.3 ± 0.6 [77]	19.1 ± 0.5 [89]	0.55
Serum TSH (mU/L)				
Geometric $\bar{x}$	5.5 [41]	2.9 [84]	2.6 [99]	<0.001[5]
Limits[6]	4.6–6.6	2.7–3.1	2.4–2.8	
Urinary iodine (μg/L)				
Geometric $\bar{x}$	11 [37]	202 [67]	216 [83]	<0.001[5]
Limits[6]	9–13	180–227	192–244	
Serum selenium (μg/L)				
Geometric $\bar{x}$	13.4 [42]	14.1 [67]	13.8 [86]	0.77
Limits[6]	12.6–14.3	13.5–14.7	13.3–14.4	
Serum GPX (U/L)				
Geometric $\bar{x}$	200 [41]	226 [88]	220 [100]	0.59
Limits[6]	181–221	212–239	205–235	

[1] T_4, thyroxine; T_3, triiodothyronine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; GPX, glutathione peroxidase activity.
[2] One-way ANOVA or chi-square test. The Scheffe multiple comparison test was used to compare pairs of means.
[3] $\bar{x}$ ± SE.
[4] *n* in brackets.
[5] Unsupplemented subjects compared with placebo- and iodine-supplemented subjects and selenium and iodine-supplemented subjects.
[6] Values 1 SE below and 1 SE above the mean on the logarithmic scale.

Clinical and radiologic outcomes

Clinical outcomes after 12 mo in the unsupplemented, placebo-iodine, and selenium-iodine groups are shown in **Table 2**. Frequencies of joint pain, decreased joint mobility, and morning joint stiffness did not differ significantly between the placebo-iodine group and the selenium-iodine group. The number of subjects with morning joint stiffness was significantly higher in the unsupplemented group than in the selenium-iodine group. Radiologic improvement was poor and did not differ significantly between the 3 groups. Three subjects, all belonging to the placebo-iodine group, showed new radiologic lesions at follow-up; however, comparison with the selenium-iodine group was not significant (3 of 71 in the placebo-iodine group compared with 0 of 90 in the selenium-iodine group; $P = 0.08$, Fisher exact test).

TABLE 2
Clinical outcomes after 12 mo in unsupplemented subjects with Kashin-Beck disease and in iodine-supplemented subjects with Kashin-Beck disease who were assigned to receive placebo or selenium

Characteristic	Unsupplemented	Placebo and iodine	Selenium and iodine	P[1]
Weight (kg)	24.7 ± 1.2[2] [41][3]	27.2 ± 0.9 [88]	27.3 ± 0.8 [108]	0.22
Height (cm)	124 ± 2 [41]	128 ± 2 [88]	129 ± 1 [108]	0.20
Skeletal delay (y)	2.9 ± 0.3 [39]	2.8 ± 0.1 [84]	2.9 ± 0.1 [104]	0.76
Joint pain during the past 24 h [*n* (%)]	6 (15)	13 (15)	21 (19)	0.63
Decreased joint mobility [*n* (%)]	7 (17)	16 (18)	25 (23)	0.50
Morning joint stiffness [*n* (%)]	7 (17)	6 (7)	4 (4)	0.018[4]
Scale of clinical severity [*n* (%)]				
Stage I	34 (83)	74 (84)	85 (79)	0.83
Stage II or III	7 (17)	14 (16)	23 (21)	0.83
Clinical improvement [*n* (%)]	1 (2)	4 (5)	7 (7)	0.46
Radiologic improvement [*n* (%)]	0 (0)	0 (0)	1 (0.1)	1

[1] One-way ANOVA or chi-square test. The Scheffe multiple comparison test was used to compare pairs of means.
[2] $\bar{x}$ ± SE.
[3] *n* in brackets.
[4] Unsupplemented subjects compared with placebo- and iodine-supplemented subjects and selenium- and iodine-supplemented subjects.

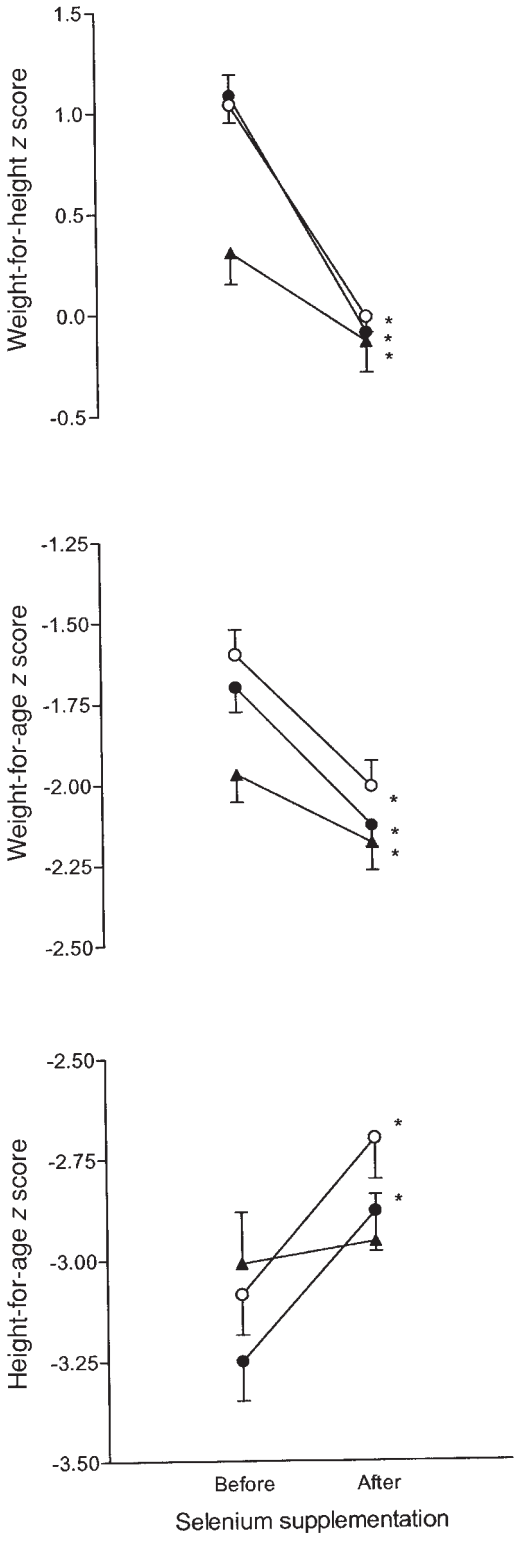

FIGURE 3. Mean (±SE) weight-for-height, weight-for-age, and height-for-age z scores before and after 12 mo of selenium supplementation in unsupplemented subjects (▲), placebo-iodine–supplemented subjects (○), and selenium-iodine–supplemented subjects (●). In two-factor repeated-measures ANOVA, the main effect of time was significant ($P < 0.001$), as was the time × iodine interaction (weight-for-height z score, $P < 0.001$; weight-for-age z score, $P = 0.026$; height-for-age z score, $P = 0.001$). *Significantly different from the baseline value, $P < 0.001$.

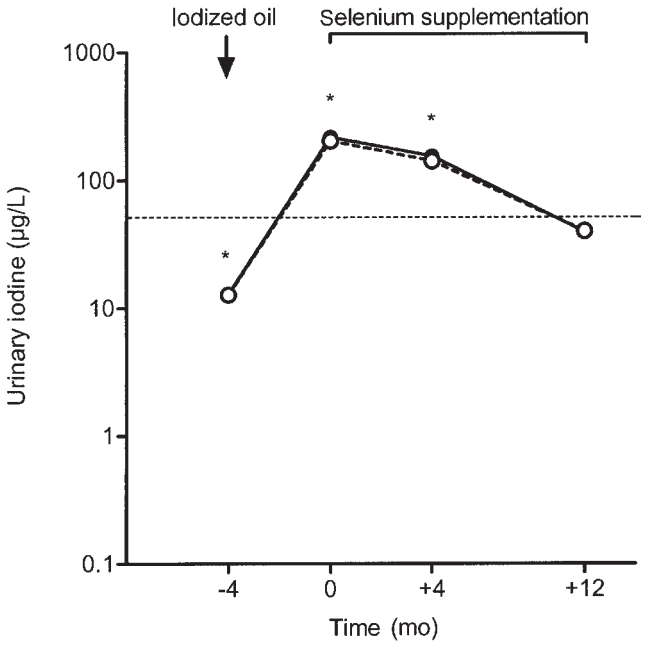

FIGURE 4. Mean urinary iodine concentrations in the placebo-iodine–supplemented subjects (○) and the selenium-iodine–supplemented subjects (●) from 4 mo before to 12 mo after selenium supplementation. The reference range for urinary iodine concentrations is located above the dotted line. There was a significant main effect of time ($P < 0.001$). *Significantly different from all subsequent values, $P < 0.001$ (Helmert contrast).

Weight-for-height, weight-for-age, and height-for-age z scores in the 3 groups before and after the 12-mo supplementation period are shown in **Figure 3**. The placebo-iodine– and selenium-iodine–supplemented children showed a significant increase in height-for-age z score, but the unsupplemented children did not. Weight-for-height and weight-for-age z scores decreased significantly in the 3 groups, suggesting that linear growth in the placebo-iodine– and selenium-iodine–supplemented children was not accompanied by appropriate weight gain.

Iodine and selenium status

The urinary iodine concentrations observed in the placebo-iodine and selenium-iodine groups are shown in **Figure 4**. Before iodine supplementation, the urinary iodine concentrations were ≈12 µg/L in both groups. These values increased significantly after iodine and remained within the reference range (50–250 µg/L) throughout most of the study period. However, 16 mo after iodine supplementation, they had fallen below 50 µg/L (ie, 39 µg/L in both groups).

Serum concentrations of thyroid hormones and thyrotropin in the placebo-iodine and selenium-iodine groups are shown in **Figure 5**. Serum thyroxine concentrations increased significantly 4 mo after iodine supplementation, and the concentrations were even higher at the end of the study in both groups. Serum triiodothyronine concentrations followed a pattern that mirrored that of serum thyroxine concentrations. Serum triiodothyronine concentrations decreased significantly 4 mo after iodine supplementation but increased again to preiodine concentrations at the end of the study in both groups. Serum thyrotropin concentrations, which were ≈6 mU/L before iodine supplementation, decreased significantly to ≈3 mU/L 4 mo after iodine supplementation in both

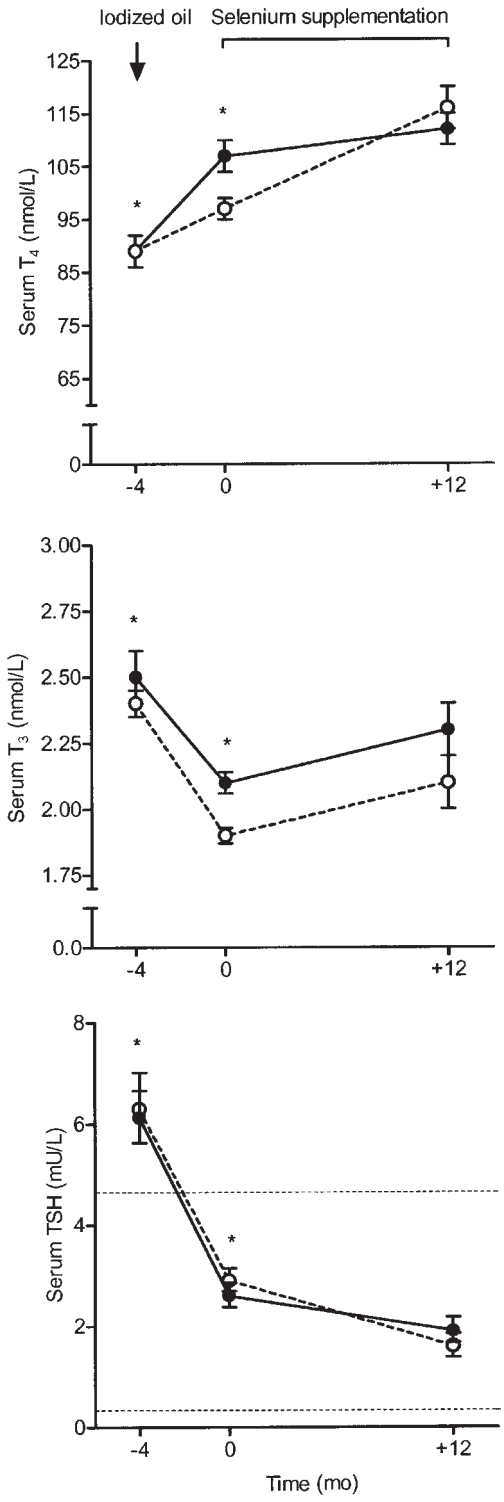

FIGURE 5. Mean (± SE) serum thyroxine (T_4), triiodothyronine (T_3), and thyrotropin (thyroid-stimulating hormone, TSH) concentrations in the placebo-iodine–supplemented subjects (○) and the selenium-iodine–supplemented subjects (●) from 4 mo before to 12 mo after selenium supplementation. The reference range for serum TSH concentrations is within the 2 dotted lines. For serum TSH, the values are means ± SEs on the logarithmic scale. A significant main effect of time was observed for serum T_4 ($P < 0.001$), T_3 ($P < 0.001$), and TSH ($P = 0.011$). *Significantly different from all subsequent values, $P < 0.001$ (Helmert contrast). For serum T_3, there was a significant main effect of group ($P = 0.03$).

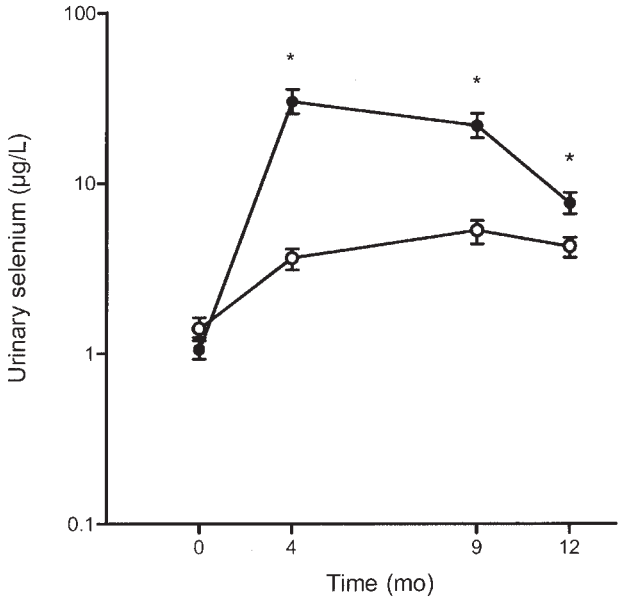

FIGURE 6. Mean (± SE on the logarithmic scale) urinary selenium concentrations in the placebo-iodine–supplemented subjects (○) and the selenium-iodine–supplemented subjects (●) during 12 mo of placebo or selenium supplementation. There was a significant main effect of time ($P < 0.001$) and a significant time × treatment interaction ($P < 0.001$). *Significantly different from placebo-iodine–supplemented subjects, $P < 0.0125$ (*t* test with Bonferroni correction).

groups. Serum thyrotropin concentrations remained within the normal range during the 12-mo supplementation period in both groups but were significantly lower at the end of the supplementation period than at the beginning (Figure 5, bottom panel). Serum thyrotropin was not significantly affected by selenium supplementation for 12 mo. Four subjects had low serum thyrotropin concentrations (< 0.3 mU/L) 4 mo after iodine supplementation. Serum thyrotropin concentrations were normal at 12 mo in the 2 subjects who accepted blood testing. Compliance with selenium supplementation was monitored by measuring urinary selenium concentrations at regular intervals (**Figure 6**). Urinary selenium concentrations increased 30-fold in the selenium-iodine group and 4-fold in the placebo-iodine group. After 12 mo of supplementation, mean serum selenium concentrations were within the reference range and were significantly greater in the selenium-iodine group than in the placebo-iodine group [61 μg/L (range: 43–85 μg/L; $n = 40$) compared with 29 μg/L (range: 17–50 μg/L; $n = 39$); $P < 0.001$]. Mean serum GPX was also significantly greater in the selenium-iodine group than in the placebo- iodine group [818 U/L (range: 629–1064 U/L; $n = 44$) compared with 442 U/L (range: 269–726 U/L; $n = 38$ subjects); $P < 0.001$]. The relations between individual values for serum selenium and GPX after selenium supplementation are shown in **Figure 7**. Most of the subjects in the selenium-iodine group had values for serum selenium and GPX within the respective reference ranges, whereas all but 2 of the subjects in the placebo-iodine group and all of the subjects in the unsupplemented group were below the reference ranges.

DISCUSSION

Selenium and iodine deficiency are endemic in Tibet (5). Whereas iodine deficiency is known to cause endemic goiter and

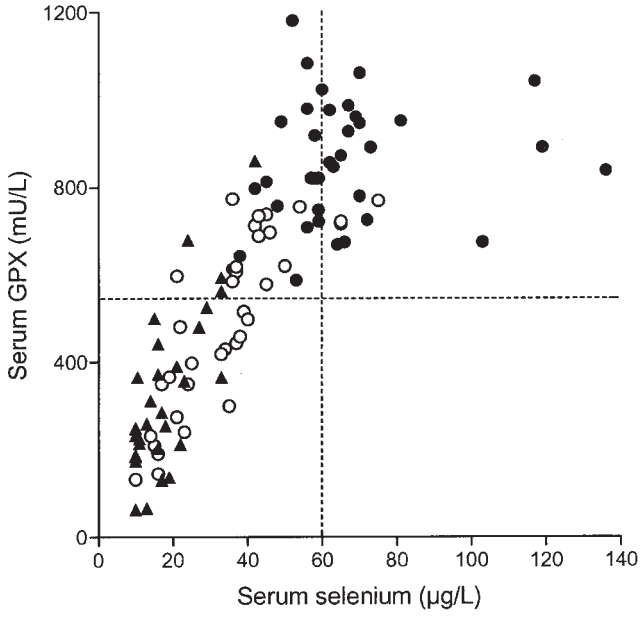

FIGURE 7. Relation between serum glutathione peroxidase activity (GPX) and serum selenium concentration after selenium supplementation in unsupplemented subjects (▲), placebo-iodine–supplemented subjects (○), and selenium-iodine–supplemented subjects (●). Serum selenium and GPX were significantly correlated for serum selenium concentrations < 60 μg/L ($r = 0.77$, $P < 0.001$) but not for concentrations > 60 μg/L ($r = 0.05$, $P = 0.81$). There were significant correlations between serum selenium and GPX in the unsupplemented subjects ($r = 0.82$, $P < 0.001$), the placebo-iodine–supplemented subjects ($r = 0.83$, $P < 0.001$), and the selenium-iodine–supplemented subjects ($r = 0.34$, $P = 0.04$). The dotted lines indicate the lower reference value for serum selenium concentrations and GPX.

cretinism, the effect of selenium deficiency on health remains uncertain, particularly in relation to Kashin-Beck disease. Because selenium supplementation was shown to prevent Keshan disease, a cardiomyopathy endemic in selenium-deficient areas of China, it was proposed that Kashin-Beck disease might also be related to low selenium status (4). The present study differs in several ways from previous studies (13, 14): it was designed as a double-blind, randomized controlled trial; the criteria for inclusion in the trial were standardized; and, because selenium may aggravate hypothyroidism in selenium- and iodine-deficient subjects, iodine deficiency was first corrected (7). Previously performed trials in China included only subjects with radiologic lesions, but only 14% of the subjects who met the clinical criteria for Kashin-Beck disease in the present study showed radiologic lesions. Persons with radiologic lesions have more advanced stages of the disease and are expected to be less influenced by selenium treatment than are persons without radiologic lesions. In the present study, 12 mo of selenium supplementation of subjects affected by Kashin-Beck disease had no effect on the main symptoms and signs, ie, joint pain and decreased joint mobility. The study does not exclude the possibility that selenium may prevent the occurrence of Kashin-Beck disease in unaffected children from endemic areas or the occurrence of new lesions in affected children, because new radiologic lesions occurred in the placebo-iodine group only. Growth retardation diminished significantly in both the placebo-iodine group and the selenium-iodine group but not in the unsupplemented group, and this effect was probably due to the correction of iodine deficiency. Selenium supplementation had no additional effect on stunting once iodine deficiency was corrected. Interestingly, the improved growth in the iodine-supplemented children was not accompanied by an increase in body weight. Study subjects in the 3 groups had lower weight-for-height and weight-for-age *z* scores after the 12-mo supplementation period. This probably reflects a decrease in food availability in the region, because the unsupplemented group showed a similar pattern (15). The correction of iodine deficiency thus appeared to stimulate growth in children affected by Kashin-Beck disease, notwithstanding a situation of overall food scarcity. This study shows that a single dose of 475 mg I could correct severe iodine deficiency in iodine- and selenium-deficient subjects for up to 1 y. Sixteen months after iodine administration, serum thyroxine and thyrotropin concentrations were within their respective reference ranges, despite the fact that urinary iodine concentrations were below the reference range. Four subjects had transient biochemical hyperthyroidism. This adverse reaction cannot be completely avoided after iodine supplementation, but the incidence should be reduced by administering low doses of iodine and by avoiding iodine treatment of subjects with large nodular goiter. In any case, the adverse effects of a transient iodine-induced hyperthyroidism must be balanced against the risk of long-standing hypothyroidism due to uncorrected iodine deficiency, particularly in children and pregnant women (16, 17).

After 12 mo of selenium supplementation, serum selenium concentrations in the selenium-iodine group were within the reference range and were significantly greater than those in the placebo-iodine group. The monitoring of compliance allowed us to detect a moderate increase in urinary selenium concentrations in the placebo-iodine group. The source of this increase is unclear, but some of the subjects in the placebo-iodine group may have received selenium tablets from the Tibetan health authorities. Recycling of excreted selenium, similar to the recycling of iodine observed in Nepal, where living conditions are similar, may also have contributed to this result (18). Urinary selenium excretion increased 30-fold from the baseline values, and serum selenium concentrations were within the reference range in the selenium-iodine group. The observed relation between serum selenium and GPX substantiates the biological efficiency of selenium treatment. The strong correlation between these 2 variables in the unsupplemented and placebo-iodine–supplemented subjects (Figure 7) reflects the inadequacy of their selenium status. In contrast, the weak correlation in the selenium-iodine–supplemented subjects shows the successful correction of deficiency, as shown by the sufficiency of selenium status for satisfaction of GPX in serum (19). Therefore, we estimated that the apparent introduction of some exogenous selenium into the community during the study did not preclude a valid comparison.

The effects of selenium supplementation on thyroid hormone metabolism have been studied extensively in selenium-deficient animals (20–25), but few studies are available on the effects of low selenium status on thyroid hormone metabolism in humans (26–28). Our data show that after 12 mo of selenium supplementation, there were no significant differences in serum concentrations of thyroid hormones and thyrotropin between the placebo-iodine and selenium-iodine groups. This finding supports the findings of previous studies that suggest a moderate effect of selenium deficiency on thyroid hormones (27, 29). The thyroid gland, like other endocrine organs, retains selenium, and hence deiodinase

activities in these tissues are maintained (30). This might explain the negligible effect of selenium deficiency on thyroid hormone metabolism. In conclusion, selenium supplementation had no effect on growth or thyroid function in patients with Kashin-Beck disease once iodine deficiency was corrected. The present data do not support the use of selenium supplementation for the treatment of subjects with Kashin-Beck disease. Therefore, iodine but not selenium deficiency should be corrected in Tibetan children with Kashin-Beck disease.

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