

KASHIN-BECK OSTEOARTHROPATHY IN RURAL TIBET IN RELATION TO SELENIUM AND IODINE STATUS

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ABSTRACT

Background and Methods Kashin-Beck disease is a degenerative osteoarticular disorder that is endemic to certain areas of Tibet, where selenium deficiency is also endemic. Because selenium is involved in thyroid hormone metabolism, we studied the relation among the serum selenium concentration, thyroid function, and Kashin-Beck disease in 575 subjects 5 to 15 years of age in 12 villages around Lhasa, Tibet, including 1 control village in which no subject had Kashin-Beck disease. Clinical, radiologic, and biochemical data were collected.

Results Among the 575 subjects, 280 (49 percent) had Kashin-Beck disease, 267 (46 percent) had goiter, and 7 (1 percent) had cretinism. Of the 557 subjects in whom urinary iodine was measured, 66 percent had a urinary iodine concentration of less than 2 μg per deciliter (157 nmol per liter; normal, 5 to 25 μg per deciliter [394 to 1968 nmol per liter]). The mean urinary iodine concentration was lower in subjects with Kashin-Beck disease than in control subjects (1.2 vs. 1.8 μg per deciliter [94 vs. 142 nmol per liter], $P < 0.001$) and hypothyroidism was more frequent (23 percent vs. 4 percent, $P = 0.01$). Severe selenium deficiency was documented in all villages; 38 percent of subjects had serum concentrations of less than 5 ng per milliliter (64 nmol per liter; normal, 60 to 105 ng per milliliter [762 to 1334 nmol per liter]). When age and sex were controlled for in a multivariate analysis, low urinary iodine, high serum thyrotropin, and low serum thyroxine-binding globulin values were associated with an increased risk of Kashin-Beck disease, but a low serum selenium concentration was not.

Conclusions In areas where severe selenium deficiency is endemic, iodine deficiency is a risk factor for Kashin-Beck disease. (N Engl J Med 1998;339:1112-20.)

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KASHIN-BECK disease is an osteoarthropathy of uncertain cause that is endemic in Tibet and other areas of China, Siberia, and North Korea — areas where selenium deficiency is also endemic.¹ Affected subjects have varying degrees of joint deformation and limited joint mobility. In the most severe cases, there is necrosis of growth plates and joint cartilage, resulting in decreased limb length and short stature. Osteoarthropathy usually becomes evident between the ages of 5 and 15 years.

The disorder is probably of environmental origin. It has been reported in white migrants to the areas of endemic disease,¹ and clinical and radiologic improvement occurs in children who move to areas where the disease is not endemic.^{2,3} Selenium deficiency has been suggested as a risk factor for this disease, because selenium concentrations in the serum of subjects living in areas where Kashin-Beck disease is endemic and in the food they eat are lower than the respective values in areas without endemic disease.⁴⁻⁶ However, the efficacy of selenium supplements in the prevention of Kashin-Beck disease is controversial.^{6,7}

In most regions of China in which selenium deficiency is endemic, iodine deficiency is also endemic, but the converse is not true.⁸ Because hypothyroidism impairs skeletal development in children,^{9,10} we hypothesized that iodine deficiency and Kashin-Beck disease might be associated. In this study we evaluated the iodine and selenium status of Tibetan subjects with Kashin-Beck disease.

METHODS

Study Design and Subjects

In May 1995, in Lhasa Prefecture, Tibet, we conducted a survey in 11 villages (total number of inhabitants, 1686) in which Kashin-Beck disease was reported by the health authorities and 1 (with 293 inhabitants) in which it was not. The latter village was situated 40 km from the nearest village in which some subjects were affected. The study protocol was approved by the Lhasa Health Bureau of Tibet and the institutional review board of the Ambroise Paré Hospital of Mons, Belgium. Two study-team members made a census of the population of each village by means of household visits and invited the parents of all subjects 5 to 15 years of age to bring them to the health center. Informed consent was obtained from the parents. In the villages with Kashin-Beck disease, 502 subjects were recruited out of a total target group of 608 (83 percent), and in the control village, 73 of 77 subjects (95 percent) were recruited.

Clinical Examination

Kashin-Beck disease was diagnosed when a subject who was 5 to 15 years old and lived in an area where the disease was en-

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demically had persistent pain, limitation of motion, or deformity of the knees, ankles, elbows, wrists, interphalangeal joints, hips, or shoulders, as shown by physical examination, and did not have local inflammation or a history of trauma.¹¹ Goiter was classified according to the World Health Organization criteria, as follows: stage 0, no goiter; stage Ia, goiter detectable only by palpation and not visible even when the neck is fully extended; stage Ib, palpable goiter visible only when the neck is fully extended; and stage II, goiter visible with the neck in the normal position.¹² Cretinism was diagnosed on the basis of physical examination when a subject living in an area of severe iodine deficiency had mental deficiency and either a predominant neurologic syndrome, including defects of hearing and speech, squint, and characteristic disorders of stance and gait of varying degree, or predominant hypothyroidism and growth retardation.¹³ A height-for-age index was calculated for each subject with the use of standard reference tables.¹⁴

Laboratory Measurements

Blood samples were obtained for measurement of selenium, thyroxine, triiodothyronine, thyroxine-binding globulin, thyrotropin, and glutathione peroxidase activity in serum. Urine samples were collected for measurement of iodine. The samples were frozen within eight hours and kept frozen until analysis within two months in Belgium.

Serum selenium was measured by atomic-absorption spectrometry with the Zeeman background correction (model Z3030, Perkin-Elmer, Überlingen, Germany), with a limit of sensitivity of 5 ng per milliliter (64 nmol per liter); undetectable concentrations were assigned a value of 5 ng per milliliter.¹⁵ Glutathione peroxidase activity was measured spectrophotometrically ($\lambda = 340$ nm) by the decrease in NADPH (0.28 mmol per liter) at 37°C on a biochemical analyzer (Hitachi 717, Boehringer Mannheim, Mannheim, Germany), with aromatic organic peroxide (isopropylbenzene [cumene] hydroperoxide; final concentration, 0.18 mmol per liter) and glutathione (final concentration, 4 mmol per liter) as substrates in 0.05 mol per liter of phosphate buffer (pH, 7.2) and 4.3 mmol per liter of EDTA in the presence of excess glutathione reductase (≥ 0.05 mol per liter). The limit of sensitivity for the detection of serum glutathione peroxidase was 50 U per liter; samples with undetectable enzyme activity were assigned this value. Serum thyroxine, triiodothyronine, and thyrotropin were measured with use of an automated immunoassay with chemiluminescence detection (ACS 180, Corning, Los Angeles) and commercial reagents. Serum thyroxine-binding globulin was measured by radioimmunoassay with commercial kits (RIA, Biocode, Liège, Belgium). Urinary iodine was measured with a Technicon AutoAnalyzer (Technicon, Tarrytown, N.Y.) with a limit of sensitivity of 0.6 μg per deciliter (47 nmol per liter).¹⁶

Quality control for trace-element analysis was performed by comparison with reference standards and participation in an interlaboratory comparison study.¹⁷ The reference values for normal adults in Belgium were as follows: serum thyroxine, 6.0 to 12.0 μg per deciliter (77 to 154 nmol per liter); triiodothyronine, 80 to 195 ng per deciliter (1.2 to 3.0 nmol per liter); thyroxine-binding globulin, 12 to 26 mg per liter; thyrotropin, 0.3 to 4.6 mU per liter; selenium, 60 to 105 ng per milliliter (762 to 1334 nmol per liter); glutathione peroxidase activity, 550 to 1100 U per liter; and urinary iodine, 5 to 25 μg per deciliter (394 to 1968 nmol per liter). Hypothyroidism was defined as a serum thyrotropin concentration greater than 10 mU per liter.

Radiologic Evaluation

Radiographs of the right hand and foot were taken with portable x-ray equipment. The films were rated by a pediatric radiologist who was unaware of the clinical status of the subject. Skeletal maturity was assessed by the method of Greulich and Pyle.¹⁸ Bone-age delay was calculated as chronologic age minus radiologic bone age. Distinguishing between the radiologic findings in subjects

with hypothyroidism and those with Kashin-Beck disease can be difficult. In hypothyroidism, the shortening of the long bones is generalized and homogeneous, the ossification of the epiphyses is spotty and irregular, and the metaphyses are wide and irregular. In Kashin-Beck disease, the shortening of the long bones of the legs is asymmetric, the ossification of the epiphyses is normal, the deformity is progressive, and the metaphyseal deformities are more pronounced. To be given a radiologic diagnosis of Kashin-Beck disease, the subject had to have at least one of the following: irregular erosions of the 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 epiphyses, premature closure of metaphyses with subsequent shortening of metacarpal or metatarsal bones and phalanges, or talus collapse with osteosclerosis.

Statistical Analysis

For serum thyrotropin, selenium, and glutathione peroxidase and for urinary iodine, the geometric means (\pm SD) are given because the log-transformed values fit a normal distribution better than the untransformed values. The results were analyzed by one-way analysis of variance and chi-square tests. Within the villages where Kashin-Beck disease was endemic, odds ratios adjusted for age and sex were estimated, with 95 percent confidence intervals, by logistic-regression analysis for the association of demographic and biologic variables with Kashin-Beck disease. Continuous variables were converted to three categories based on division of the sample into three equal groups or on commonly used cutoff values. Statistical analyses were performed with SPSS software (SPSS, Chicago). All statistical tests were two-sided.

RESULTS

Among the 557 subjects from the 12 villages in Lhasa Prefecture in whom urinary iodine was measured, 365 (66 percent) had urinary iodine values of less than 2 μg per deciliter (157 nmol per liter), levels indicative of severe iodine deficiency (Fig. 1). The serum selenium concentrations in 521 subjects from these 12 villages are shown in Figure 2; 197 (38 percent) had undetectable values (< 5 ng per milliliter).

The study subjects were divided into three groups according to their base-line demographic and clinical characteristics: subjects with Kashin-Beck disease, subjects without Kashin-Beck disease who lived in villages where the disease was endemic, and subjects from the control village (Table 1). Among all 575 subjects, 49 percent had Kashin-Beck disease. Within the 11 villages in which Kashin-Beck disease was endemic, this proportion ranged from 13 percent to 100 percent. Boys were more frequently affected than girls ($P < 0.001$), and the subjects with Kashin-Beck disease were slightly older than those without it. The proportions of subjects with delayed bone age and growth retardation were similar in the three groups. However, the children with Kashin-Beck disease who were older than 12 years were significantly shorter than the unaffected children (mean [\pm SD] height-for-age z score, -3.5 ± 1.1 [82 subjects] vs. -2.8 ± 1.0 [37 subjects]; $P = 0.009$).

Among the 575 subjects, 267 (46 percent) had goiter. The proportion of subjects with goiter was higher in the villages with Kashin-Beck disease than in the control village (Table 1). Most subjects (92

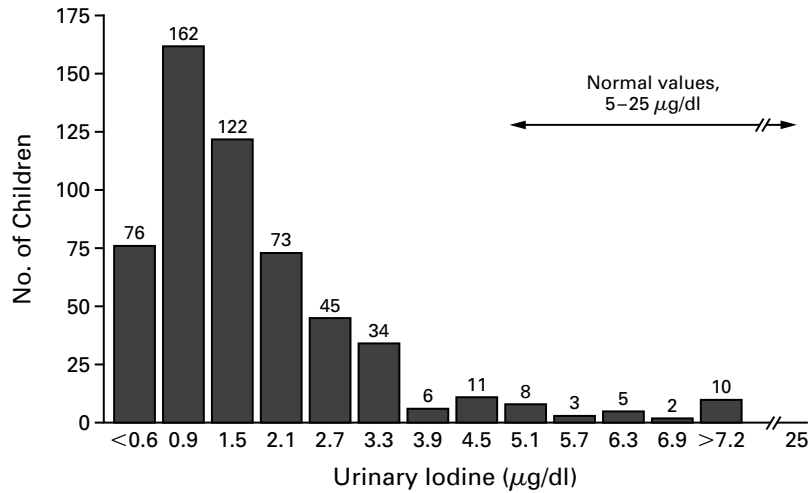


Figure 1. Distribution of Urinary Iodine Concentrations in 557 Subjects from 12 Villages in Lhasa Prefecture, Tibet.

Fourteen percent had urinary iodine concentrations $<0.6 \mu\text{g}$ per deciliter, 66 percent had concentrations $<2 \mu\text{g}$ per deciliter, and 95 percent had concentrations $<5 \mu\text{g}$ per deciliter. The numbers on the horizontal axis represent the midpoints of the intervals shown. To convert values for urinary iodine to nanomoles per liter, multiply by 78.7.

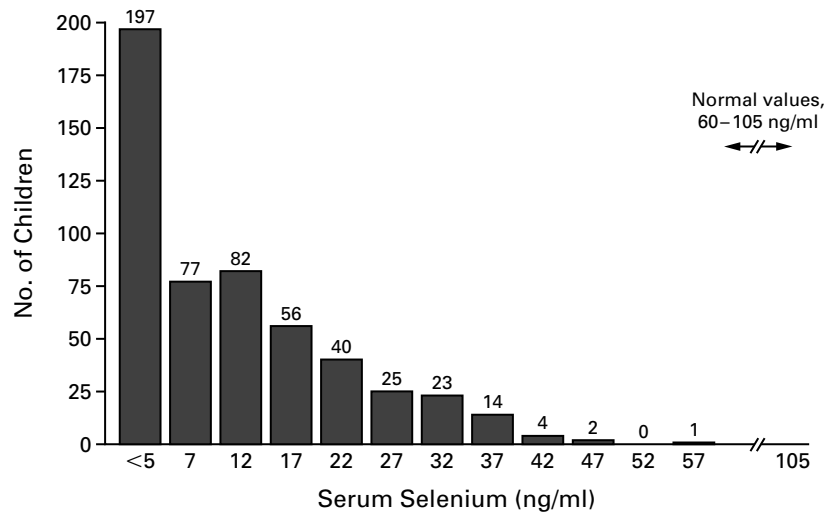


Figure 2. Distribution of Serum Selenium Concentrations in 521 Subjects from 12 Villages in Lhasa Prefecture, Tibet.

Thirty-eight percent had serum selenium concentrations $<5 \text{ ng}$ per milliliter, 50 percent had concentrations $<8.7 \text{ ng}$ per milliliter, and 89 percent had concentrations $<27 \text{ ng}$ per milliliter. The numbers on the horizontal axis represent the midpoints of the intervals shown. To convert values for serum selenium to nanomoles per liter, multiply by 12.7.

percent) had small goiters (stage Ib), and only 8 percent had stage II goiters. In the villages with Kashin–Beck disease, seven of the subjects (1 percent) had cretinism, as compared with none in the control village. In the villages with Kashin–Beck disease, 105 subjects (23 percent) had a serum thyrotropin concentration greater than 10 mU per liter, and 21

(5 percent) had a concentration greater than 50 mU per liter, as compared with 3 subjects (4 percent) and none, respectively, in the control village (Table 1). The percentages of subjects with low serum thyroxine and serum triiodothyronine concentrations were higher in the villages where Kashin–Beck disease was endemic than in the control village. The

TABLE 1. BASE-LINE CHARACTERISTICS OF SUBJECTS WITH KASHIN-BECK DISEASE AND UNAFFECTED SUBJECTS LIVING IN VILLAGES WHERE KASHIN-BECK DISEASE IS ENDEMIC AND SUBJECTS LIVING IN THE CONTROL VILLAGE.*

| CHARACTERISTIC | SUBJECTS WITH DISEASE IN VILLAGES WITH KASHIN-BECK DISEASE (N=280) | | SUBJECTS WITHOUT DISEASE IN VILLAGES WITH KASHIN-BECK DISEASE (N=222) | | SUBJECTS WITHOUT DISEASE IN CONTROL VILLAGE (N=73) | | P VALUE |
|---|--|-----------------|---|-----------------|--|-----------------|---------|
| | VALUE | NO. OF SUBJECTS | VALUE | NO. OF SUBJECTS | VALUE | NO. OF SUBJECTS | |
| Age — yr | 10±3 | 280 | 9±3 | 222 | 9±3 | 73 | <0.001† |
| Male sex — no. (%) | 173 (62) | | 94 (42) | | 38 (52) | | <0.001† |
| Skeletal delay — yr | 2.6±1.3 | 270 | 2.6±1.4 | 196 | 2.4±1.3 | 71 | 0.35 |
| Height-for-age z score | -3.2±1.0 | 279 | -3.2±1.4 | 218 | -3.1±1.0 | 73 | 0.87 |
| Goiter — no. (%) | 136 (49) | | 115 (52) | | 16 (22) | | 0.001‡ |
| Serum thyroxine — µg/dl | 7.1±2.6 | 259 | 7.5±2.8 | 201 | 8.6±2.3 | 72 | 0.001‡ |
| Serum thyroxine <6 µg/dl — no. (%) | 79 (31) | | 55 (27) | | 8 (11) | | 0.004‡ |
| Serum triiodothyronine — ng/dl | 163±33 | 257 | 167±32 | 201 | 170±26 | 72 | 0.21 |
| Serum triiodothyronine <150 ng/dl — no. (%) | 98 (38) | | 58 (29) | | 14 (19) | | 0.005‡ |
| Serum thyroxine-binding globulin — mg/liter | 18.6±3.5 | 268 | 20.2±3.7 | 204 | 20.3±3.3 | 72 | <0.001† |
| Serum thyroxine-binding globulin <18 mg/liter — no. (%) | 121 (45) | | 52 (25) | | 14 (19) | | <0.001† |
| Serum thyrotropin — mU/liter | | | | | | | |
| Geometric mean | 6.3 | | 5.9 | | 3.9 | | <0.001‡ |
| Limits§ | 2.5-15.9 | 262 | 2.3-15.3 | 202 | 2.3-6.5 | 72 | |
| Serum thyrotropin >10 mU/liter — no. (%) | 61 (23) | | 44 (22) | | 3 (4) | | 0.001‡ |
| Urinary iodine — µg/dl | | | | | | | |
| Geometric mean | 1.2 | | 1.6 | | 1.8 | | <0.001† |
| Limits§ | 0.6-2.7 | 273 | 0.7-3.4 | 212 | 1.0-3.2 | 72 | |
| Urinary iodine <1 µg/dl — no. (%) | 98 (36) | | 52 (25) | | 10 (14) | | <0.001† |
| Serum selenium — ng/ml | | | | | | | |
| Geometric mean | 10.3 | | 8.8 | | 11.5 | | 0.009¶ |
| Limits§ | 5.1-20.8 | 265 | <5.0-16.7 | 201 | 5.8-22.9 | 55 | |
| Serum selenium <5 ng/ml — no. (%) | 94 (35) | | 86 (43) | | 17 (31) | | 0.15 |
| Serum glutathione peroxidase — U/liter | | | | | | | |
| Geometric mean | 210 | | 153 | | 294 | | <0.001 |
| Limits§ | 96-458 | 207 | 75-309 | 147 | 184-471 | 63 | |
| Serum glutathione peroxidase <100 U/liter — no. (%) | 47 (23) | | 43 (29) | | 0 | | <0.001‡ |

*P values were derived from one-way analysis of variance or by the chi-square test with Yates' correction. The Scheffé multiple-comparison test was used to compare pairs of means. To convert values for serum thyroxine to nanomoles per liter, multiply by 12.87. To convert values for serum triiodothyronine to nanomoles per liter, multiply by 0.01536. To convert values for urinary iodine to nanomoles per liter, multiply by 78.7. To convert values for serum selenium to nanomoles per liter, multiply by 12.7. Plus-minus values are means ±SD.

†The value for the affected subjects in the villages with endemic disease differs significantly from the values for the unaffected subjects in the villages with endemic disease and the control village.

‡The values for the affected and unaffected subjects in the villages with endemic disease differ significantly from that for the subjects in the control village.

§These values represent the values 1 SD below and 1 SD above the mean on the logarithmic scale.

¶The value for the unaffected subjects in the villages with endemic disease differs significantly from those for the subjects with Kashin-Beck disease and those in the control village.

||The values for the three groups differ significantly from one another.

percentage of subjects with low serum concentrations of thyroxine-binding globulin was higher among those with Kashin-Beck disease than among the unaffected subjects in the same villages or the subjects in the control village. The mean urinary iodine concentration was significantly lower in the subjects with Kashin-Beck disease than in the other

two groups. Serum selenium concentrations and glutathione peroxidase activity were low in all three groups, but they were lowest in the unaffected subjects living in the villages where Kashin-Beck disease was endemic.

The association between iodine deficiency and Kashin-Beck disease persisted when age and sex

TABLE 2. RISK OF KASHIN-BECK DISEASE IN VILLAGES WHERE THE DISEASE IS ENDEMIC, ACCORDING TO THYROID FUNCTION.*

| VARIABLE | NO. OF SUBJECTS | NO. OF CASES OF DISEASE (%) | ADJUSTED OR (95% CI) | P VALUE FOR TREND |
|---|-----------------|-----------------------------|----------------------|-------------------|
| Age (yr) | | | | <0.001 |
| 5-7 | 158 | 62 (39) | 1.0 | |
| 8-11 | 178 | 103 (58) | 1.8 (1.1-2.9) | |
| 12-15 | 166 | 115 (69) | 3.1 (1.9-5.1) | |
| Sex | | | | |
| Female | 267 | 107 (40) | 1.0 | |
| Male | 235 | 173 (74) | 2.3 (1.6-3.4) | |
| Serum selenium (ng/ml) | | | | 0.082 |
| ≤5 | 185 | 97 (52) | 1.0 | |
| 5.1-15.0 | 147 | 79 (54) | 0.9 (0.6-1.4) | |
| ≥15.1 | 134 | 89 (66) | 1.6 (1.0-2.6) | |
| Urinary iodine (μg/dl) | | | | 0.007 |
| <1.0 | 150 | 98 (65) | 1.0 | |
| 1.0-1.9 | 182 | 101 (55) | 0.7 (0.4-1.1) | |
| ≥2.0 | 153 | 74 (48) | 0.5 (0.3-0.8) | |
| Serum thyroxine (μg/dl) | | | | 0.10 |
| <6.0 | 134 | 79 (59) | 1.0 | |
| 6.0-8.9 | 200 | 119 (60) | 1.0 (0.6-1.6) | |
| ≥9.0 | 126 | 62 (49) | 0.6 (0.4-1.1) | |
| Serum triiodothyronine (ng/dl) | | | | 0.71 |
| <150 | 156 | 98 (63) | 1.0 | |
| 150-174 | 155 | 78 (50) | 0.6 (0.4-1.0) | |
| ≥175 | 147 | 81 (55) | 0.9 (0.6-1.5) | |
| Serum thyrotropin (mU/liter) | | | | 0.03 |
| <5 | 217 | 113 (52) | 1.0 | |
| 5-10 | 142 | 88 (62) | 1.6 (1.0-2.5) | |
| >10 | 105 | 61 (58) | 1.6 (1.0-2.7) | |
| Serum thyroxine-binding globulin (mg/liter) | | | | 0.001 |
| <17.0 | 125 | 91 (73) | 1.0 | |
| 17.0-19.9 | 159 | 85 (53) | 0.4 (0.2-0.7) | |
| ≥20.0 | 188 | 92 (49) | 0.4 (0.2-0.7) | |

*Odds ratios for urinary iodine concentration and serum thyroxine, triiodothyronine, thyrotropin, and thyroxine-binding globulin concentrations have been adjusted for age, sex, and serum selenium concentration. Odds ratios for serum selenium concentrations have been adjusted for age, sex, and urinary iodine concentration. To convert values for serum thyroxine to nanomoles per liter, multiply by 12.87. To convert values for serum triiodothyronine to nanomoles per liter, multiply by 0.01536. To convert values for urinary iodine to nanomoles per liter, multiply by 78.7. To convert values for serum selenium to nanomoles per liter, multiply by 12.7. OR denotes odds ratio, and CI confidence interval.

were controlled for by multivariate analysis (Table 2). The risk of Kashin-Beck disease was higher for subjects with lower urinary iodine concentrations and higher serum thyrotropin concentrations. The association of selenium deficiency with Kashin-Beck disease was not significant in the multivariate analysis.

The most frequent sign of Kashin-Beck disease was deformation of at least one joint, most often in the leg (Table 3). The frequency of joint deformation and limitation of motion increased with age, but the frequency of joint pain did not.

Among 271 subjects with clinically diagnosed cases of Kashin-Beck disease, 41 (15 percent) had radiologically confirmed cases (radiographs were missing in 9 cases), with more radiologically confirmed cases among older children than among younger children. Only two of the clinically unaffected subjects (1 percent) had radiologic abnormalities. Figure 3 compares the radiographs of the hand and an-

kle of a 14-year-old boy with Kashin-Beck disease and a normal Tibetan boy of the same age.

Among the 39 subjects with radiologically confirmed Kashin-Beck disease in whom serum selenium and urinary iodine excretion were measured, 21 (54 percent) had serum selenium concentrations of less than 5 ng per milliliter, 12 (31 percent) had hypothyroidism, and 15 (38 percent) had urinary iodine concentrations of less than 1 μg per deciliter (79 nmol per liter). The geometric mean serum selenium concentration (7.7 ng per milliliter [98 nmol per liter]) and level of serum glutathione peroxidase activity (131 U per liter) were both significantly lower than the values in the subjects living in the control village (P=0.006 and P<0.001, respectively).

DISCUSSION

Signs of Kashin-Beck disease were common in subjects living in the study area; however, neither

TABLE 3. FREQUENCY OF JOINT ABNORMALITIES IN 280 SUBJECTS WITH KASHIN-BECK DISEASE.

| CATEGORY OF SUBJECTS | DEFORMATION | PAIN | LIMITATION OF MOTION | ABNORMAL RADIOGRAPHIC FINDINGS |
|--|-------------|--------|----------------------|--------------------------------|
| | | | | |
| Subjects with abnormality of any joint, according to age | | | | |
| All | 95 | 58 | 21 | 15 |
| 5-8 yr | 87 | 56 | 6 | 6 |
| 9-12 yr | 99 | 57 | 19 | 12 |
| 13-15 yr | 99 | 63 | 40 | 30 |
| P value for trend | <0.001 | 0.610 | <0.001 | <0.001 |
| Subjects with abnormality of legs | | | | |
| Knee | | | | |
| Total | 75 | 44 | 10 | |
| Unilateral | 3 | 13 | 2 | |
| Ankle | | | | |
| Total | 70 | 40 | 6 | |
| Unilateral | 3 | 14 | 1 | |
| P value for knee vs. ankle | 0.51 | 0.30 | 0.21 | |
| Subjects with abnormality of arms or hands | | | | |
| Elbow | | | | |
| Total | 52 | 16 | 14 | |
| Unilateral | 6 | 7 | 3 | |
| Interphalangeal joints | | | | |
| Total | 2 | 0.4 | 0.4 | |
| Unilateral | 0 | 0 | 0 | |
| Wrist | | | | |
| Total | 1 | 1 | 1 | |
| Unilateral | 0 | 0 | 0.4 | |
| P value for elbow vs. interphalangeal joints or wrist | <0.001 | <0.001 | <0.001 | |

the clinical signs nor the radiologic findings are specific for the disease. Fifteen percent of clinically diagnosed cases of Kashin-Beck disease were confirmed radiologically, and the frequency of radiologic abnormalities increased with age, rising to 30 percent among the 13-to-15-year-old subjects. Despite the low frequency of radiographic abnormalities, as compared with that in previous studies,¹⁹ we consider the clinical classification of the disease to be valid, for two reasons. First, the quality of the radiographs did not permit the detection of early signs, such as minimal irregular erosions and other subtle changes in interphalangeal joints.¹⁹ Second, a pediatric radiologist who was blinded to the clinical findings found lesions compatible with Kashin-Beck disease in 41 of the 271 subjects with clinically diagnosed Kashin-Beck disease who were evaluated, but in only 2 of the 277 children without signs of Kashin-Beck disease. Therefore, we based the subsequent analysis on the clinical classification of the disease and considered radiologically confirmed cases to represent more advanced stages.

Selenium deficiency is more severe in China than in Central Africa²⁰ or New Zealand.^{21,22} A compilation of reference values for serum selenium²³ revealed

a large geographic variation that could be linked to variations in the availability of dietary selenium.²⁴ For example, the mean serum selenium concentration is about 40 ng per milliliter (508 nmol per liter) in normal adults in Eastern Europe and 200 ng per milliliter (2540 nmol per liter) in the United States.²³ Serum selenium concentrations vary according to age, with lower concentrations in children.^{23,25}

The severity of selenium deficiency in the study subjects was corroborated by the low level of serum glutathione peroxidase activity. Glutathione peroxidase is a selenium-containing enzyme, and serum glutathione peroxidase is a marker of selenium abundance.²² A threshold concentration of selenium exists below which there is a linear association between the serum selenium concentration and glutathione peroxidase activity, indicating the interdependence of these measurements. In a study of Belgian children, the threshold for optimal serum glutathione peroxidase activity was a serum selenium concentration of 55 ng per milliliter (696 nmol per liter).²⁶ In other studies, the serum selenium concentrations that corresponded to optimal glutathione peroxidase activity measured in platelets were 95 to 135 ng per milliliter (1207 to 1715 nmol per liter).²⁷



Figure 3. Radiographs of the Left Hand and Left Ankle of a 14-Year-Old Boy with Kashin–Beck Disease (Panels A and B) and of the Left Hand and Left Ankle of a Normal 14-Year-Old Tibetan Boy (Panels C and D, Facing Page).

The carpal bones of the boy with Kashin–Beck disease are small and irregular, the articular spaces are narrow, and the carpal length is reduced. The metacarpal bones are short, and their proximal ends are widened. The metaphyses of the phalanges are widened, and the middle phalanx is fragmented, with a cone-shaped epiphysis. The tarsal bones have an irregular, collapsed aspect, the tarsal length is decreased, and the metatarsal bones are shortened and have irregular proximal ends. The distal epiphysis of the tibia is cone-shaped, and there is premature closure of the metaphysis, with subsequent shortening of the tibia.

Iodothyronine deiodinases are selenoproteins involved in the deiodination of thyroid hormones.²⁸ In a study in animals, selenium deficiency had only slight effects on serum thyroid hormone concentrations, despite a marked decrease in deiodinase activity in the liver.²⁹ In the selenium- and iodine-deficient subjects in Tibet, the mean serum thyroxine and triiodothyronine concentrations were within the normal ranges in all groups. The increase in the activity of type I deiodinase in the thyroid in association with iodine deficiency, the preferential secretion of triiodothyronine by the iodine-deficient thyroid gland, and the capacity of the thyroid to conserve selenium are the main mechanisms mitigating the

effects of selenium and iodine deficiency on thyroid-hormone secretion.²⁹

Our observations extend to Tibet the conclusions of previous epidemiologic surveys. The geographic distribution of Kashin–Beck disease covers a large belt from northeastern to southwestern China that is characterized by severe selenium deficiency, with a population mean serum selenium concentration of less than 20 ng per milliliter (254 nmol per liter).²¹ The geographic association between Kashin–Beck disease and selenium deficiency was first reported in the 1970s,³ but Kashin–Beck disease does not occur in every selenium-deficient area in China. Selenium deficiency alone has not so far been demonstrated to



C



D

cause any disease. Even Keshan disease, a selenium-responsive cardiomyopathy endemic in China, is not fully explained by low selenium status.³⁰ For individual subjects within the severely selenium-deficient group we studied, we found no direct evidence of selenium status as a risk factor for Kashin-Beck disease. Other environmental factors, such as oxidative stress due to mycotoxins contaminating cereals, might have a role.³¹

Iodine deficiency, hypothyroidism, and low serum concentrations of thyroxine-binding globulin were significantly related to Kashin-Beck disease in this study. The association with serum thyroxine-binding globulin could be accounted for by protein-calorie malnutrition, a marker of risk for Kashin-Beck disease. Hypothyroidism secondary to iodine deficiency results in epiphyseal dysgenesis, delay of osseous development, and reduced endochondral ossification,^{10,11} and it probably contributes to the clinical features of Kashin-Beck disease in Tibet.

Kashin-Beck disease and iodine-deficiency disor-

ders remain major public health problems in rural Tibet. Iodine-supplementation programs should be extended without delay. However, the effect of selenium deficiency on Kashin-Beck disease remains to be established, and studies of the efficacy of selenium supplementation are needed. If selenium supplementation proves effective, it is important to correct iodine deficiency first in order to avoid aggravating hypothyroidism.³²

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REFERENCES

1. Sokoloff L. The history of Kashin-Beck disease. *N Y State J Med* 1989; 89:343-51. [Erratum, *N Y State J Med* 1989;89:486.]
2. *Idem*. Acquired chondronecrosis. *Ann Rheum Dis* 1990;49:262-4.
3. Allander E. Kashin-Beck disease: an analysis of research and public health activities based on a bibliography 1849-1992. *Scand J Rheumatol Suppl* 1994;99:1-36.
4. Wu J, Xu GL. Plasma selenium content, platelet glutathione peroxidase and superoxide dismutase activity of residents in Kashin-Beck disease affected area in China. *J Trace Elem Electrolytes Health Dis* 1987;1:39-43.
5. Yang GO, Ge KY, Chen JS, Chen XS. Selenium-related endemic diseases and the daily selenium requirement of humans. *World Rev Nutr Diet* 1988;55:98-152.
6. Yang GQ, Xia YM. Studies on human dietary requirements and safe range of dietary intakes of selenium in China and their application in the prevention of related endemic diseases. *Biomed Environ Sci* 1995;8:187-201.
7. Peng A, Yang C, Rui H, Li H. Study on the pathogenic factors of Kashin-Beck disease. *J Toxicol Environ Health* 1992;35:79-90.
8. Ma T, Guo J, Wang F. The epidemiology of iodine-deficiency diseases in China. *Am J Clin Nutr* 1993;57:Suppl:264S-266S.
9. Delange F, Ermans AM, Vis HL, Stanbury JB. Endemic cretinism in Idjwi Island (Kivu Lake, Republic of the Congo). *J Clin Endocrinol Metab* 1972;34:1059-66.
10. Vanderpas JB, Rivera-Vanderpas MT, Bourdoux P, et al. Reversibility of severe hypothyroidism with supplementary iodine in patients with endemic cretinism. *N Engl J Med* 1986;315:791-5.
11. Mathieu F, Begaux F, Lan ZY, Suetens C, Hinsenkamp M. Clinical manifestations of Kashin-Beck disease in Nyemo Valley, Tibet. *Int Orthop* 1997;21:151-6.
12. Thilly CH, Delange F, Stanbury JB. Epidemiological surveys in endemic goiter and cretinism. In: Stanbury JB, Hetzel BS, eds. *Endemic goiter and endemic cretinism: iodine nutrition in health and disease*. New York: John Wiley, 1980:157-83.
13. Definitions of endemic goiter and cretinism, classification of goiter size and severity of endemias, and survey techniques. In: Dunn JT, Pretelle EA, Hernán Daza C, Viteri FE, eds. *Towards the eradication of endemic goiter, cretinism, and iodine deficiency*. Washington, D.C.: Pan American Health Organization, 1986:373-80. (Scientific publication no. 502.)
14. WHO Working Group. Use and interpretation of anthropometric indicators of nutritional status. *Bull World Health Organ* 1986;64:929-41.
15. Nève J, Chamart S, Molle L. Optimization of a direct procedure for the determination of selenium in plasma and erythrocytes using Zeeman effect atomic absorption spectroscopy. In: Brätter P, Schramel P, eds. *Trace element — analytical chemistry in medicine and biology*. Vol. 4. Berlin, Germany: Walter de Gruyter, 1987:349-58.
16. Vanderpas J, Bourdoux P, Lagasse R, et al. Endemic infantile hypothyroidism in a severe endemic goitre area of central Africa. *Clin Endocrinol (Oxf)* 1984;20:327-40.
17. Nève J, Thomassen Y, Van Damme M. Cooperative study on measurement of concentrations of selenium in freeze-dried (human whole) blood. *Pure Appl Chem* 1992;64:765-80.
18. Greulich WW, Pyle SI. *Radiographic atlas of skeletal development of hand and wrist*. Stanford, Calif.: Stanford University Press, 1959.
19. Wang Y, Yang Z, Gilula LA, Zhu C. Kashin-Beck disease: radiographic appearance in the hands and wrists. *Radiology* 1996;201:265-70.
20. Vanderpas J, Contempré B, Duale NL, et al. Iodine and selenium deficiency associated with cretinism in northern Zaire. *Am J Clin Nutr* 1990; 52:1087-93.
21. Diplock AT. Trace elements in human health with special reference to selenium. *Am J Clin Nutr* 1987;45:Suppl:1313-22.
22. *Idem*. Indexes of selenium status in human populations. *Am J Clin Nutr* 1993;57:Suppl:256S-258S.
23. Alifhan G, Nève J. Reference values for serum selenium in various areas — evaluated according to the TRACY protocol. *J Trace Elem Med Biol* 1996;10:77-87.
24. Nève J. Methods in determination of selenium states. *J Trace Elem Electrolytes Health Dis* 1991;5:1-17.
25. Lombeck I, Kasperek K, Harbisch HD, Feinendegen LE, Bremer HJ. The selenium state of healthy children. I. Serum selenium concentration at different ages: activity of glutathione peroxidase of erythrocytes at different ages: selenium content of food of infants. *Eur J Pediatr* 1977;125:81-8.
26. Calomme MR, Vanderpas JB, François B, et al. Thyroid function parameters during a selenium repletion/depletion study in phenylketonuric subjects. *Experientia* 1995;51:1208-15.
27. Nève J. Human selenium supplementation as assessed by changes in blood selenium concentration and glutathione peroxidase activity. *J Trace Elem Med Biol* 1995;9:65-73.
28. St Germain DL, Galton VA. The deiodinase family of selenoproteins. *Thyroid* 1997;7:655-68.
29. Meinhold H, Campos-Barros A, Walzog B, Köhler R, Müller F, Behne D. Effects of selenium and iodine deficiency on type I, type II, and type III iodothyronine deiodinases and circulating thyroid hormone in the rat. *Exp Clin Endocrinol* 1993;101:87-93.
30. Beck MA, Kolbeck PC, Rohr LH, Shi Q, Morris VC, Levander OA. Benign human enterovirus becomes virulent in selenium-deficient mice. *J Med Virol* 1994;43:166-70.
31. Chasseur C, Suetens C, Nolard N, Begaux F, Haubruge E. Fungal contamination in barley and Kashin-Beck disease in Tibet. *Lancet* 1997;350: 1074.
32. Contempré B, Dumont JE, Ngo B, Thilly CH, Diplock AT, Vanderpas J. Effect of selenium supplementation in hypothyroid subjects of an iodine and selenium deficient area: the possible danger of indiscriminate supplementation of iodine-deficient subjects with selenium. *J Clin Endocrinol Metab* 1991;73:213-5.