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Age-related Reference Values for Serum Selenium Concentrations in Infants and Children

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Background: **Children are at particular risk for selenium deficiency, which has potentially serious medical implications. Reliable age-specific reference values for serum selenium concentrations in children are sparse, but are essential for the identification of selenium deficiency and decisions regarding selenium supplementation.**

Methods: **Using electrothermal atomic absorption spectrometry, we analyzed serum selenium concentrations from 1010 apparently healthy children (age range, 1 day to 18 years) and from 60 patients on a protein-restricted diet because of inborn errors of metabolism. Reference intervals were defined according to recommended guidelines.**

Results: **Medians for serum selenium concentrations showed a statistically significant age dependency: a decrease from the age <1 month (0.64 μmol/L) to 4 months (0.44 μmol/L); an increase to 0.62 μmol/L in the 4–12 months age group; constant values in children between 1 and 5 years of age (0.90 μmol/L); and an additional slight increase to reach a plateau between 5 and 18 years (0.99 μmol/L). Of 43 children older than 1 year and on a protein-restricted diet, 87% showed serum selenium concentrations below the 2.5 percentile.**

Conclusions: **Because of nutritional changes, serum selenium concentrations are significantly higher in older children than in infants under 1 year of age. The application of age-adjusted reference values may provide more specific criteria for selenium supplementation. Long-term protein restriction in children is reflected by a failure to achieve higher serum selenium concentrations with increasing age.**

There is increasing evidence that selenium plays an important role in mammalian metabolism. Selenium deficiency may have several serious short- and long-term medical implications, such as cardiomyopathy, cardiovascular disease, male infertility, impaired immune response, or even cancer *(1)*. On the other hand, selenium is not an innocuous micronutrient; it is also known as a highly toxic agent. Acute or chronic selenium poisoning may lead to skin and hair abnormalities and gastrointestinal or neurologic symptoms *(2, 3)*. Reliable data on reference values in healthy individuals are needed to help identify patients displaying serum selenium deficiency and for decision-making concerning selenium supplementation.

Theoretically, several factors may contribute to variations in serum selenium concentrations. These include short-term physiologic influences, such as food quality and intake, as well as long-term influences, such as age, sex, and race. In addition, serum selenium concentrations are thought to exhibit regional differences and to be strongly influenced by geologic and geochemical factors (i.e., drinking water and locally produced food) *(4)*. Therefore, potential "regional" variations need to be verified. Populations at risk for developing selenium deficiency are patients with total or partial parenteral nutrition, individuals on low-protein and therefore low-selenium diets, patients with chronic diseases that lead to malabsorption, or patients with oncologic disorders. In general, the pediatric population is considered more likely to be at risk for selenium deficiency. Because of nutritional changes after birth, serum selenium concentrations are expected to be much more heterogeneous in this group than in an adult population. The sample size needed for establishment of reliable reference values in children is therefore much larger than the sample size

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required for adults. This is particularly true when percentiles must be determined *(5)*. Large numbers of blood samples from carefully characterized healthy children are difficult to obtain. For this reason, many previous studies on selenium concentrations in children have investigated only small cohorts. To our knowledge, only one study from Canada *(6)* and one from France *(7)* were evaluated according to generally accepted guidelines.

One particular group of children at risk for developing selenium deficiency includes patients suffering from inborn errors of metabolism that necessitate a therapeutic reduction of the daily intake of natural protein. The diets of these children consist mainly of food containing very low amounts of selenium: vegetables, fruit, and low-protein bread and pasta in combination with amino acid mixtures free of precursor amino acids for the single enzyme defect. Nutrients containing higher amounts of selenium, such as meat, seafood, eggs, and whole-grain products, cannot be included in the diet because of their high protein content. The mean selenium intake of dietetically treated patients, e.g., with phenylketonuria, amounts to <20% of that of healthy children *(8)*.

In this study, the analysis of serum selenium concentrations in a large cohort of apparently healthy German children allowed us to establish age-specific reference intervals according to IFCC recommendations. As an example for clinical decision-making, serum selenium concentrations from 60 patients treated with a low-protein diet because of an inborn error of metabolism were also analyzed in a pilot study.

Materials and Methods

STUDY POPULATION

A total of 1010 apparently healthy children (532 boys and 478 girls; age range, 1 day to 18 years) were included in the study. Of these, 166 children were younger than 1 year (see Fig. 1). The study followed the guidelines of the Helsinki Declaration of 1975 as revised in 1996 regarding the use of human subjects. The patients were visiting the outpatient department or a surgical ward of the University Children's Hospital in Munich, Germany, for blood analysis during a routine health check or before elective surgery (e.g., inguinal herniotomy). Fifteen infants, ages 1–7 days, were seen by a pediatrician in the nursery of the Department of Obstetrics, University of Munich, for routine newborn examinations or evaluation of physiologic jaundice. All children were metabolically healthy, on a regular balanced diet, and in good nutritional condition. None had fever; signs of infection; gastrointestinal, cardiac, or renal disease; tumors; or hematologic, neurologic, neuromuscular, or myopathic disease. Exclusion criteria included chronic illnesses, particular dietary habits, or intake of trace-element-containing preparations *(9)*.

In addition, we investigated 60 children suffering from inborn errors of metabolism on a low-protein diet (phenylketonuria; organic acidurias, such as methylmalonic aciduria, propionic acidemia, and isovaleric acidemia; tyrosinemia type 1; and urea cycle defects). They visited the specialized outpatient department at the University Children's Hospital in Munich, Germany.

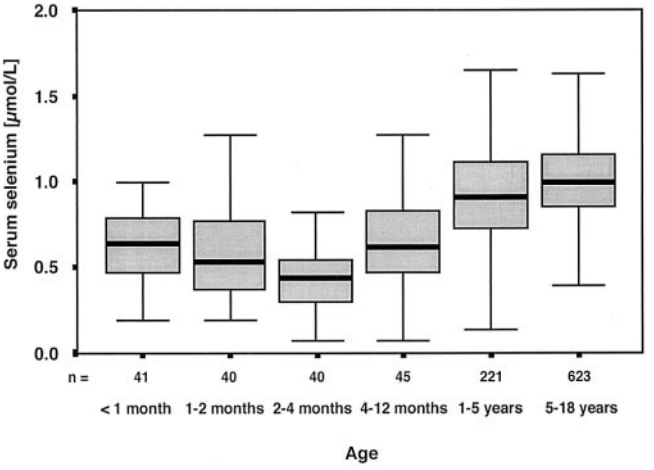

Fig. 1. Serum selenium concentrations for different age groups.

The *boxes* represent the 50% confidence interval (25–75 percentiles); the *horizontal black bar* represents the median; the *error bars* indicate the minimum–maximum range, excluding outliers. Outliers are beyond the range of 1.5 times the size of the box. Age groups were compared by ANOVA. Results for the above age categories differed significantly from each other in all cases ($P < 0.01$).

COLLECTION OF BLOOD SAMPLES

Blood was either drawn or allowed to drip freely into plain serum tubes (Microvette 500 Serum; cat. no. 20.1343; Sarstedt), depending on the age of the patients. After centrifugation (1.500*g* for 10 min), serum samples were kept in polystyrene tubes (cat. no. 55.475 from Sarstedt) and stored at −20 °C until analysis. Hemolyzed samples were excluded from the study. Utmost care was taken to avoid all potential preanalytical contamination during specimen acquisition. Because we did not find differences in serum selenium concentrations between samples obtained after an overnight fast and those obtained postprandially, participants were included in the study regardless of the time period between blood sampling and the last meal. No individual had fasted longer than 12 h. Recommendations for collection of venous blood from children with special reference to production of reference values *(10)* were followed as closely as possible.

CHEMICALS

The SPEX 1000 mg/L (12.7 mmol/L) selenium solution was obtained from SPEX Chemical. Palladium(II) nitrate dihydrate (40% Pd), "pro synthesis" quality, and hydrochloric acid were from Merck. Magnesium nitrate hexahydrate (ACS quality) was from Aldrich Chemical Co, and Triton X-100 was from Sigma. The following reference materials were used: Seronorm™ Trace Elements Serum (Accurate Chemical & Scientific Corp.), Nycomed serum batch 112 (Nycomed Pharma), and ClinCheck Level I and Level II (Recipe Chemical and Instruments).

INSTRUMENTATION

Selenium determinations were performed on a PE 5000 atomic absorption spectrometer equipped with a graphite furnace and autosampler (Perkin-Elmer).

SELENIUM ANALYSES

Selenium was measured by electrothermal atomic absorption spectrometry (ET-AAS), using a pyrolytic tube as described previously *(11)*. Samples were analyzed without digestion by use of palladium matrix modification. The matrix modifier contained palladium nitrate (1 g/L), hydrochloric acid (32 mL/L), magnesium nitrate (1 g/L), and Triton X (0.1 mL/L) in water.

Serum samples (150 μL) were divided into three equal parts, and 0, 10 (0.127 μmol), or 20 μL (0.254 μmol) of the SPEX 1000 mg/L (12.7 mmol/L) selenium solution were added to each 50-μL aliquot. The modifier solution was then added to each aliquot (450, 440, or 430 μL, respectively), giving a modifier (including selenium solution): sample ratio of 10:1 by volume. These three modifier/serum aliquots with added selenium solution were then measured by ET-AAS at a wavelength of 196 nm. The temperature program used included a drying step (100 °C), an ashing step (250 °C), and an atomizing step (2000 °C for 3 s). The injection volume was 10 μL. For quantification of results, the standard addition technique was applied.

STATISTICAL ANALYSIS

Statistical analysis was carried out with SPSS software (Ver. 10.0.7) from SPSS Inc. The check for gaussian distribution was performed with the Kolmogorov–Smirnoff test. Group differences were identified with the Mann–Whitney *U*-test for nongaussian-distributed groups or with the two-tailed Student *t*-test for gaussian-distributed groups.

Results

LINEARITY, PRECISION, DETECTION LIMIT, AND ACCURACY

We confirmed the linearity of the assay by adding the SPEX 1000 mg/L (12.7 mmol/L) selenium solution to serum samples from healthy children. The calibration curves were linear up to 3.81 μmol/L.

The intraassay precision was assessed by analyzing a pooled serum sample. The CV was 7.1% (n = 22; mean ± SD, 1.14 ± 0.08 μmol/L). In comparison, two series of serum-free modifier samples with selenium added (0.635 and 1.27 μmol/L) yielded CVs of 5.5% (mean ± SD, 0.70 ± 0.038 μmol/L) and 2.6% (mean ± SD, 1.28 ± 0.033 μmol/L). The interassay precision was assessed by analyzing two in-house reference materials prepared with serum-modifier samples to which selenium had been added to final concentrations of 1.27 and 2.54 μmol/L. The interassay CVs were 7.4% (n = 27; mean ± SD, 1.16 ± 0.086 μmol/L) and 6.9% (n = 23; mean ± SD, 2.47 ± 0.17 μmol/L), respectively.

Blank values were 0.0146 ± 0.0036 μmol/L (mean ± SD; n = 11), giving a detection limit (signal + 5 SD of a sample free of analyte) for the assay of 0.018 μmol/L and a quantification limit (signal + 10 SD of a sample free of analyte) of 0.036 μmol/L.

The accuracy of the analysis was assessed by analyzing four commercially available freeze-dried serum reference materials: Nycomed batch 112, ClinCheck Level I and Level II, and Seronorm. The results obtained by analyzing the reference materials were in close agreement with the target concentration values given by the manufacturers. These materials, however, do not represent a perfect matrix match for the analysis of serum samples. Liquid serum reference materials with certified selenium concentration target values are not available at present.

Data verification was carried out by applying a second method, high-resolution inductively coupled plasma mass spectrometry, after pressure digestion of serum samples in ultrapure nitric acid. When we compared the mean selenium concentrations for a serum series previously analyzed by ET-AAS, the measured mean method ratio between high-resolution inductively coupled plasma mass spectrometry and ET-AAS was 1.02 and the related CV was 11% (n = 18).

SERUM SELENIUM CONCENTRATIONS IN HEALTHY CHILDREN AND IN PATIENTS ON A LOW-PROTEIN DIET

A total of 1010 children from a healthy pediatric population were included in the study. The serum selenium concentrations analyzed in the entire group of samples followed a gaussian distribution. No gender-related differences were detected [mean for boys (n = 532), 0.91 μmol/L; mean for girls (n = 478), 0.94 μmol/L; $P = 0.208$; data not shown]. For subsequent evaluation, gender discrimination was therefore disregarded.

For subgrouping according to age, the population was initially divided into monthly groups when <1 year of age and into yearly groups when >1 year of age. These subgroups were then tested for significant differences in their mean serum selenium concentrations. Age-related subgroups were defined when a significant statistical difference from the neighboring age group was found. Age groups that did not differ significantly in their mean serum selenium concentrations were combined and recalculated to define age-specific reference intervals.

The serum selenium concentrations for different age groups are shown in Fig. 1. In general, serum selenium was significantly lower in children younger than 1 year of age than in older children. We identified a statistically significant age dependency with a decrease from age <1 month (median, 0.64 μmol/L) to the age of 4 months (median, 0.44 μmol/L) and an increase to a median of 0.62 μmol/L in the age group between 4 and 12 months. Between the ages of 1 and 5 years, values were constant (median, 0.90 μmol/L), followed by an additional slight increase to reach a plateau between the age of 5 and 18 years (median, 0.99 μmol/L). Percentiles for serum sele-

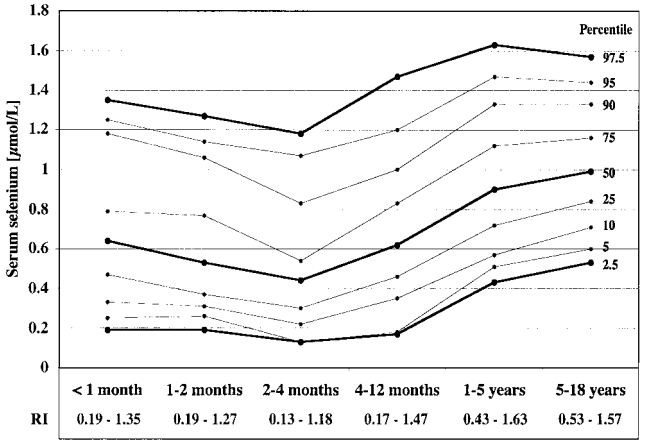

Fig. 2. Age-specific reference intervals (*RI*) based on the 2.5 and 97.5 percentiles of data derived from a healthy pediatric population for selenium concentrations in serum.

All values are given in µmol/L.

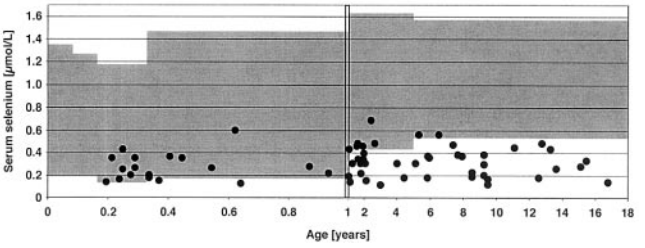

Fig. 3. Serum selenium concentrations in samples from 60 children on a protein-restricted diet.

The *shaded area* represents the age-specific intervals (2.5–97.5 percentiles) defined in this study.

nium concentrations and the resulting reference intervals for the different age groups were determined by the nonparametric method and are given in Fig. 2. The reference intervals are given as the central 95% interval bounded by the 2.5 and 97.5 percentiles.

Serum selenium concentrations from 60 patients treated with a low-protein diet showed that, despite a protein-restricted diet, in infancy serum selenium concentrations were mostly (87%) within the reference intervals established in this study. In contrast, of the children older than 1 year who were on a protein-restricted diet, only 13% showed selenium concentrations within the reference intervals (Fig. 3). Serum selenium concentrations from children on a low-protein diet belonging to different age groups did not show statistically significant differences ($P = 0.2–0.79$; data not shown).

Discussion

Selenium has moved from a biochemical curiosity to a recognized trace element and has been shown to play an important role in different aspects of mammalian metabolism. Selenium deficiency may have serious medical implications *(1)*, and supplementation is indicated under specific circumstances. Because the range between beneficial and potential toxic effects might be narrow, it could be critical to be aware of both the lower and the upper limits of the reference interval. However, when dealing with trace elements, deviations from a reference interval do not by themselves define either toxicity or deficiency. Some earlier studies in children *(12–17)* reported reference values defined only by statistical means and simple standard deviations, thus producing a narrow reference interval. This bears a considerable risk in interpreting serum selenium concentrations as falsely low, as is also the case when reference intervals derived from adults are applied. In our hospital, we have experienced unsubscripted selenium supplementation in several cases because of the application of non-age-adjusted reference values. In addition, we have repeatedly observed serum selenium concentrations above the 97.5 percentile defined in this study when patients were receiving trace element supplementation in conjunction with semisynthetic diets. Long-term chronic toxicity cannot be excluded in these cases. Some studies dealing with serum selenium concentrations in healthy pediatric populations have already pointed to an age dependency *(12, 18, 19)*. The large sample size analyzed in this study now allows a more specific definition of age-related reference intervals. Median serum selenium concentrations steadily decrease from birth with a minimum concentration at the age of 4 months (Fig. 1). This finding is in accordance with the observation that the selenium content of commercially available milk formula and human milk is low; the selenium content of cow's milk-based infant formulas is even lower than that of human milk *(20)*. In our study, we did not differentiate between breast-fed infants and those receiving formula milk. The increase in serum selenium concentrations observed between the age of 4 months and 1 year (Fig. 1) is most probably attributable to the higher selenium content of food introduced into the diet of healthy children (e.g., whole-grain products, eggs, and meat).

Regional differences for serum selenium concentrations attributable to differences in the selenium content of soils and grain have repeatedly been stressed *(1, 4, 21, 22)*. A statistically sound comparison of the results of serum selenium from healthy pediatric populations reported in 17 studies from 13 countries is not possible because of different experimental designs and incongruent methods of summarizing data and partly because of small cohorts. In children over 1 year of age, selenium concentrations are rather constant, and differences observed here may better reflect regional distinctions. We compared published data from children older than 1 year, using the mean serum selenium concentrations. Differences for children between countries appear to be less pronounced than those reported for adults (Table 1). Overall mean serum selenium concentrations in adults range from 0.63 to 2.5 µmol/L (ratio, 1:4) *(4)*, whereas overall mean values in children

Table 1. Comparison of studies on serum selenium concentrations in children older than 1 year of age in different countries.

Country	Overall mean,[a] μmol/L	Range of means,[b] μmol/L	n[c]	Age range, years	Reference
Austria	0.61[d]	0.43–0.76[d]	109	1–15	*(12)*
Austria	0.64	0.60–0.67	65	1–19	*(13)*
Finland	0.74	0.64–0.93	26	1–15	*(29)*
Belgium	0.76	0.51–0.83	28	1–15	*(14)*
Slovakia	0.76	0.75–0.77	891	11–18	*(30)*
France	0.79	0.77–0.81	118	2–5	*(15)*
Germany	0.83	0.58–0.93	120	1–18	*(31)*
France	0.85[d]	0.74–0.94[d]	186	3–16	*(7)*
Finland	0.87	0.87[e]	119	0.5–14.7[f]	*(23)*
England	0.94[d]	0.82–0.99[d]	70	2–16	*(32)*
Germany	0.98	0.94–1.00	844	1–18	This study
Italy	1.06	1.01–1.12	217	12–13	*(16)*
Japan	1.07	0.93–1.19	99	1–15	*(17)*
Slovenia	1.08	0.95–1.19	71	1–13	*(33)*
Germany	1.10[d]	1.04–1.17[d]	58	1–20	*(18)*
Turkey	1.13	1.09–1.17	80	1–16	*(34)*
US	1.35	1.35[e]	83	1–18	*(24)*
Canada	1.60	1.52–1.67	40	1–9	*(19)*

[a] The overall mean was calculated as the sum of the products of single age-dependent means and their respective sample numbers divided by the total sample number.
[b] Lowest and highest mean values reported in each study.
[c] Sample number.
[d] Overall median and range of medians.
[e] Only one mean value was reported.
[f] Children between 0.5 and 1 year of age were not differentiated.

range from 0.61 to 1.6 μmol/L (ratio, 1:2.6; Table 1). Selenium concentrations in children >1 year of age investigated in this study compare well with those available from children living in Austria, Belgium, Slovakia, France, other parts of Germany, Finland, England, Italy, Japan, Slovenia, and Turkey. In Finland, a national program using selenium-enriched agricultural fertilizers was carried out in 1985 to increase selenium intake and, thus, the serum selenium concentrations in the Finnish population. Selenium concentrations in healthy children from Finland determined before the beginning of the supplementation program, however, are in the range of values found in other European countries *(23)*. Higher values have been reported from the US *(24)* and Canada *(19)*. The state of knowledge on serum selenium in children calls for prospective, multicenter studies using harmonized methodologies for sampling, sample handling, analysis, and quality control for the identification of selenium deficiency states and the development of safe selenium supplementation protocols.

Our preliminary results on selenium concentrations in 60 children on a low-protein diet because of underlying inborn disorders of metabolism indicate for the first time that dietary protein restriction does not necessarily lead to low serum selenium concentrations in early infancy, whereas older children on a low-protein diet tend to have serum selenium concentrations below the reference interval. These data are explained by the fact that serum selenium concentrations of children receiving a low-protein diet do not increase with age as observed in the healthy pediatric population with unrestricted nutritional habits (Fig. 3). This observation may necessitate reconsideration of conclusions drawn from earlier studies. Lombeck et al. *(25)* showed an early decrease of serum selenium in infants on dietary protein restriction and interpreted this decrease as a consequence of the low-protein diet. When the reference intervals defined in our study are applied to these values, however, all serum selenium concentrations are still within the reference values and represent only the physiologic decrease in healthy children of this age group (<4 months). In older children on a continued low-protein diet, however, serum selenium often clearly drops below the reference values as shown in this and other studies *(25–28)*. Because these patients do not as yet show any clinical signs of selenium deficiency, the findings might be interpreted as a preclinical deficiency state. Exact criteria for selenium supplementation must still be defined.

In conclusion, we show that serum selenium concentrations in childhood display a significant age dependency. Application of the age-adjusted reference values defined here are necessary to prevent the misdiagnosis of selenium deficiency, particularly in very young infants, and to provide more precise decision criteria for selenium supplementation.

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