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Global survey of urinary selenium in children: A systematic review

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ABSTRACT

Background: Selenium (Se) is an essential element in the human body that plays an important role in numerous fundamental physiological functions. However, the distribution of Se in the environment varies widely resulting in this element being available in a large concentration range in the ecosystem, and thus, in the human body. Urinary Se is a biomarker considered to be involved in adaptive mechanisms that help prevent health problems.
Objectives: The purpose of the present study was to conduct a systematic review to identify studies reporting the status of urinary Se in healthy children and create a global map.
Methods: A literature search was conducted using MEDLINE (United States National Library of Medicine), Web of Science, Toxicology Bibliographic Information (TOXLINE), Latin-American and Caribbean Literature on Health Sciences (LILACS), and the grey literature. This study was registered in PROSPERO (international prospective register of systematic reviews) and was conducted in accordance with the PRISMA guidelines.
Results: We identified 322 relevant articles, out of which 15 were included in this systematic review. The study identified a total of 4038 healthy children worldwide with urinary Se concentrations from 7.7 to 145.0 µg/L.
Conclusion: This is a pioneering study that provides evidence for the presence of Se in the urine of healthy children; we have shown that the available data is restricted to a small number of individuals and specific groups. Furthermore, there is a lack of information on urinary Se, especially in Latin America, Africa, and Asia.

1. Introduction

Selenium (Se) is a natural constituent of the earth's crust and an essential element for human health [1], owing to its involvement in several physiological functions [2]. Deficiency of Se may lead to diseases, including muscular dystrophy, cardiovascular, immune, and reproductive disorders, as well as some types of cancer and hypothyroidism [2–5]. In contrast, Se toxicity may cause type 2 diabetes [6–8] and selenosis that manifests as alopecia, brittle nails, bad breath, fatigue, tooth cavities, and neurological problems [1,9–11].

The distribution of Se in the environment varies widely [12–14]. Seleniferous soil (> 3 mg/kg Se) occurs in areas of North America, parts of occidental Europe, China, and Venezuela [15], which reflects the influence of the natural environment on Se content in a given ecosystem [16] and the human body [17,18]. Human biomonitoring can be used to assess human exposure to chemicals, providing an important perspective for risk assessment. Exposure to Se is measured in different ways with the most common biomarker used to assess it being its concentrations in the plasma or serum [19]. However, methods to measure these concentrations are invasive and are dependent on slow responses to changes in dietary intake of Se [20,21].

On the other hand, measuring the concentration of urinary Se is a non-invasive, convenient, and economic method [22–24]. Urine is the main form of Se excretion [25,26]; approximately 50–70% of ingested Se is excreted via urine [27]. Urinary Se indicates recent exposure [21,28] and reflects an organism's capacity to regulate and eliminate excess Se within several days of consumption, therefore, it is considered an adaptive mechanism to prevent health issues [20,29]. This method has been applied in population-level surveys [30,31]. The assessment of Se in the body is very important to human health, especially for children as the difference between the essential (30 µg/day) and toxic dose (150 µg/day) for them is much smaller than that for adults (55 µg/day and 400 µg/day, respectively) [31].

People around the world are exposed to inadequate Se levels [32]. This problem is more prominent for children, who are a vulnerable population to environmental exposures, due to their physiology, rapid

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growth [33], and behavioral tendencies [34]. Moreover, concentration of Se has been reported to be lesser in children than in adults [19]. In this context, the purpose of the present study was to conduct a systematic review to identify studies reporting urinary Se in healthy children in order to create a global map that highlights Se exposure in children around the world, and thus, helps prevent health problems related to Se in the future.

2. Materials and methods

2.1. Search strategy

This study was registered with the open access database PROSPERO (international prospective register of systematic reviews) at its inception (registration number CRD4201706251; accessed from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017062514). It was conducted in accordance with the PRISMA guidelines [35] (Supplemental Material 1).

The search strategy employed here aimed to find published studies from any country in the world. The following computerized databases were searched from July 2017 to March 2018: MEDLINE (United States National Library of Medicine), Web of Science, Toxicology Bibliographic Information (TOXLINE), Latin-American and Caribbean Literature on Health Sciences (LILACS), and the grey literature. The search terms used here were "*selenium*" AND "*child* OR *children*" AND "*urinary*" OR "*urine*".

2.2. Inclusion and exclusion criteria

To be included in this review, studies published as original surveys to report urinary Se among populations of children were considered. All study designs were eligible with the exception of experimental laboratory studies. Articles were excluded, when they were selected by the search system but did not cover the outcome intended to be reviewed in our study, provided insufficient data, or had inaccessible full-texts (even after contacting with the author). We have reported urinary Se concentrations in units of micrograms per liter (μg/L), therefore, studies that reported concentrations in units of micrograms per grams of creatinine (μg/g creatinine) were excluded, considering that creatinine-based concentration is not the ideal measure [36].

2.3. Search results screening and data extraction

Level I screening of the search results included a review of all the titles and/or abstracts in consideration of the eligibility criteria. Full-text publications of any studies not eliminated at this level were retrieved for review of the full-text at Level II screening. All search results were screened by two individuals (MS and FMRSJ), who had approximately 95% agreement on inclusion or exclusion of studies. Differences were resolved by discussion and consultation with a third researcher (ALMB) as needed. Two researchers completed data extraction from all studies. One review author checked the text entries, and one independent quality control reviewer checked the numeric outcome from the studies. To find any additional relevant articles, the reference lists of all of the retrieved studies were examined. Furthermore, there were no restrictions on language, and the authors were contacted to gather information if the articles were not in English or Spanish.

Clinical trials, case-control of treatment, or environmental exposure studies were used only for the baseline data from their subjects in the control group (healthy or non-exposure). In cases of studies that reported data for children and adults, only data on urinary Se in children was used. The subjects in these studies were considered 'children' if they were less than 18-years-old. The authors were contacted when the required data were not available. For articles with more than one mean urinary Se value reported, weighted average in units of μg/L and its respective standard deviation (SD) were calculated for each study.

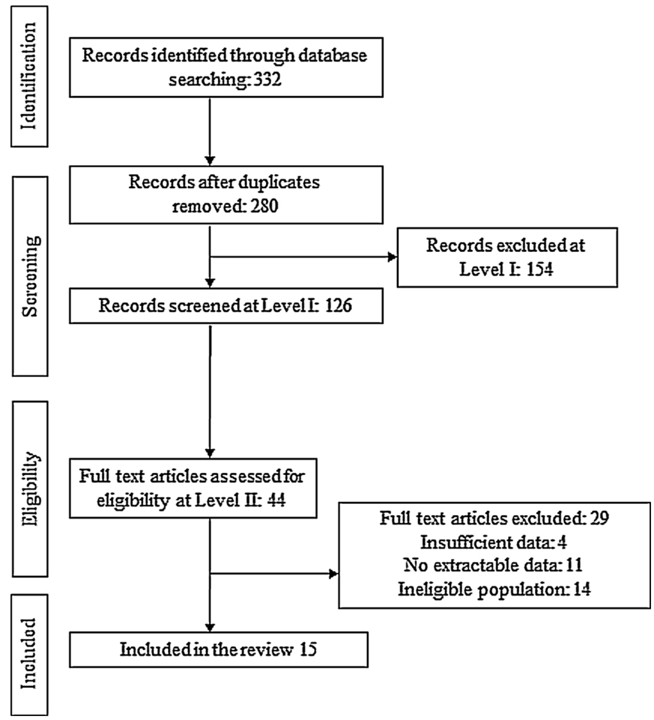

Fig. 1. Flow of information through the different phases of a systematic review.

When available, it was also extracted average in μg/L and its respective SD of serum Se concentration for each study.

To understand the prevalence of urinary Se worldwide, we drew a global map that included all studies reporting urinary Se concentrations (μg/L) in healthy children. This information was ranked according to concentrations reported for each country and colors were assigned on a scale of very high concentration (red) to very low concentration (green).

2.4. Assessment of study quality

Two reviewers (MS and FMRSJ) independently graded the methodological quality of the studies selected. They analyzed the quality of the methodology and the results (Supplemental material 2).

3. Results

The original search yielded 332 references; the supplemental search resulted in no additional references. At Level I screening based on abstracts and/or titles, 154 of the final references were excluded (Fig. 1). The most common reason for exclusion of studies at this stage of screening was that the studies did not have the outcome of interest. Full-text reports on 44 studies were retrieved for complete review at Level II. At this stage, most studies were excluded because they provided data for an ineligible population (48% studies) only, had participants with an already existing disease (27% studies), their participants were adults (19%) or had suffered from intoxication (10%), or they reported urinary Se in units of μg/g creatinine (38%). In addition, some other studies were excluded based on insufficient data (14%). Finally, after Level II screening, a total of 16 studies were included [5,26,44–49,29,37–43] and a total of 316 studies were excluded. No studies were excluded in the quality assessment.

A total of 4038 healthy children were evaluated worldwide to find out that the median urinary Se concentration in the world is 17.0 μg/L (minimum 7.7 – maximum 145.0). The main characteristics of the studies included in the systematic review are summarized in Table 1 (countries, study design, sample size, year of age, urinary Se, Se in

Table 1
Characteristics of included studies reported urinary selenium status in healthy children.

Reference	Countries	Study design	n	Year of age	Urine Se (µg/L) Mean SD		Serum Se (µg/L) Mean SD		Analytical method
	Europe								
[42]	Czech Republic	Cross-sectional	235	6 – 18	13.1	5.5	50.6	10.1	Atomic fluorescence spectrophotometer
[26]	Germany	Cross-sectional	72	2 – 17	17.0	–	–		Inductively coupled plasma mass spectroscopy
[43]	Greece	Case- Control	5	5 –10	17.0	2.0	–		Atomic fluorescence spectrophotometer
[44]	Greece	Observational	16	0 – 10	13.8	2.8	–		Atomic fluorescence spectrophotometer
[49]	Poland	Cross-sectional	40	8 – 17	57.7	10.5	106.7	8.7	Atomic absorption spectrometry with graphite furnace
	Asia								
[37]	Bangladesh	Cohort	205	5	15.4	7.7	–		Inductively coupled plasma mass spectroscopy
[29]	Bangladesh	Cohort	2765	5 – 10	14.5	6.3	–		Inductively coupled plasma mass spectroscopy
[39]	China	Case- Control	35	7 – 14	7.7	4.1	39.1	8.9	Atomic fluorescence spectrophotometer with hydride generation
[5]	Pakistan	Cross-sectional	210	3 – 12	19.3	4.3	202.5	8.4	Atomic absorption spectrometer with graphite furnace
[47]	Pakistan	Cross-sectional	76	newborn	54.7	6.5	82.3	1.6	Atomic fluorescence spectrophotometer with hydride generation
[41]	Turkey	Case- Control	84	6 –- 12	30.3	15.0	–		Atomic absorption spectrometer with Flame
[40]	Turkey	Case- Control	32	3 – 15	59.8	13.4	202.4	21.5	Inductively coupled plasma mass spectroscopy
	North America								
[46]	United States of America	Case- Control	73	10 – 18	145.0	–	–		No information
	South America								
[38]	Brazil	Clinical trial	41	2 – 6	40.0	10.0	113.99		Atomic fluorescence spectrophotometer with hydride generation
[50]	Brazil	Cross-sectional	94	6 – 11	14.9	1.3	–		Atomic absorption with graphite furnace

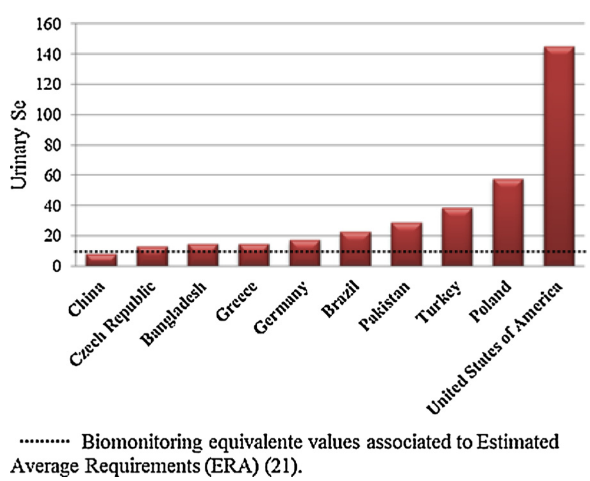

Fig. 2. Urinary Se concentration (µg/ L) in healthy children according to each country.

serum and analytical method). Eight countries had reports of urinary Se concentrations in healthy children without Se supplementation (Fig. 2). Fig. 3 demonstrates the special distribution of urinary Se in children across the world (µg/L).

4. Discussion

This study is a survey that was carried out with healthy children as subjects from all across the world to assess variability in urinary Se concentrations and to explain its possible health effects. In the past few years, concern about children's health has increased. During childhood, the body undergoes development and many factors, such as genetic background, physiology, nutrition, age, and lifestyle, influence children's health. Therefore, they are more susceptible and vulnerable to adverse health issues and need special care [34].

In this review, it was found out that the concentration range of urinary Se in children around the world is quite large. The differences are probably due to environmental factors, which can have important consequences on Se concentrations in the human body [12–14,16,17]. Studies in countries with high anthropogenic activities [51,52], including Pakistan [5], Turkey [40], Poland [49], and the United States of America [46], had reports of higher urinary Se concentrations in children. On the other hand, China had the lowest urinary Se concentrations [39] with a high prevalence of the Kashin–Beck disease, which is characteristic to low Se areas. In corroboration with the research by Schomburg [53], who reported lower Se intake in east Europe, relatively low urinary Se excretion was recorded in subjects from the Czech Republic (13.1 µl/L).

In addition to environmental factors, socioeconomic conditions and different nutrition patterns may be important for urinary Se [20] concentrations as well. For instance, children from the Amazonian region - Brazil had high urinary Se because of the high intake of the Brazilian nut [38], which is the most important food source of Se [54]. According to the literature, Se concentrations vary by gender, age [5,43,55,56], body weight, and height [29,49]. Children generally present significantly lower daily Se excretion rate and a higher Se excretion per kg of body weight than adults, which may be due to their fast growth [44,57]. Many studies have provided evidence of Se concentrations being related to health in children using urinary Se as a biomarker [58–63].

However, despite the importance of Se for children's health, it is worrisome that there is no reference value for urinary Se in this population. Urinary Se is a biomarker that can be used as a screening tool to inform risk assessment in children since it is an adaptive mechanism [20,29]. Hays et al. [21] established biomonitoring equivalent (BE) values as per the EAR (estimated average requirements) and the UL (upper limits) of urinary Se concentrations in adults (10 µg/L and 90 µg/L as per the EAR and the UL, respectively). However, the authors recommended some caution in the use of these established values as a screening value for children. Except China [39] had urinary Se concentration above the BE values as per the EAR. While none of the studies reported urinary Se concentrations to be higher than the values associated with the UL [21].

There were several limitations to our study, such as small sample, lack of a discreet study design, a lack of methodology to quantify urinary Se, and availability of only limited data; generating a global map

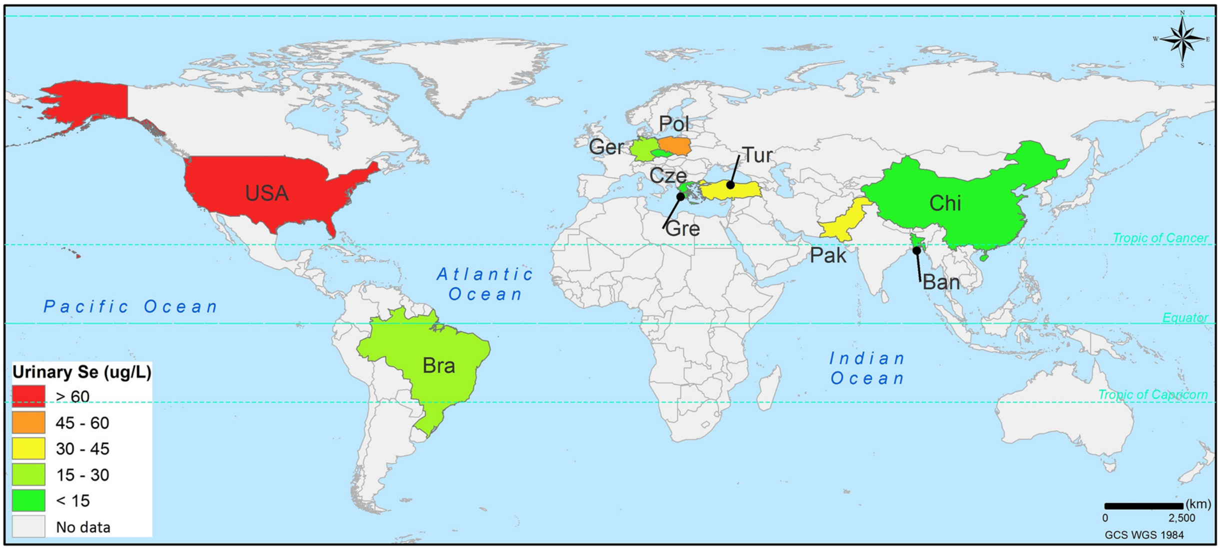

Fig. 3. Global map according to urinary Selenium status (μg/L) in healthy children.

was also a challenge. It is concerning that several countries did not have any data or information available due to limited studies on the topic making it impossible to study the influence of Se exposure in these regions [64]. Furthermore, no data was found for most of Africa, Eastern Europe, the Middle East, Central Asia, Southeast Asia, and Central and Latin America, all of which are regions, where children may suffer from Se deficiency. Indeed, it should be considered that the number of studies that were excluded at Level II because they reported data for children with an existing disease, such as Turner syndrome [60], idiopathic nephrotic syndrome [63], burn injuries [61], phenylketonuria [58,59], and cystic fibrosis [62], was quite large

Furthermore, although urinary Se concentrations were reported in many studies from different countries, these Se concentrations were acquired from the blood, plasma, or hair samples, but had no data for urine. On the other hand, a positive aspect of our study is that it used an open (in general terms) search strategy, while using a restrictive criteria for selections based on titles, abstracts, and complete article readings only, to allow for the largest possible number of studies to be included in the survey. It is important to point out that such information about urinary Se concentrations can help prevent health problems in children around the world.

5. Conclusion

To the best of our knowledge, this systematic review is a pioneer study to report urinary Se in healthy children worldwide and to investigate its variability on a global scale. We have shown that data available on the topic is restricted to a small number of individuals and specific groups of subjects. Furthermore, there is a significant lack of information on urinary Se concentrations in children, especially in Latin America, Africa, and Asia. In spite of the number and quality of studies increasing over the years, more studies are needed to confirm the usefulness of urinary Se concentrations as a biomarker, as well as to establish reference values of urinary Se in children.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2019.07.001.

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Marina Dos Santos - 28 years old - is a nutritionist and is finishing her doctorate in Health Sciences in March 2019. Her thesis on Selenium in food and biological samples in the coal region has highlighted the researcher at national and international level, with the publication of 3 articles (Dos Santos et al 2018 doi: 10.1016 / j.chemosphere.2018.01.082, Dos Santos et al 2017 doi: 10.1016 / j.jfca.2017.01.001, Da Silva Júnior et al in press) and two in the advanced stages of publication, as well as prizes received at conferences. This last study comes to crown an important research in the area of biomonitoring of trace elements with a view to environmental and human health and brings a global overview of the use of urinary biomarker for selenium research. **Corresponding:** (BR): 55-5399815825.