Original Article

SELENIUM LEVELS IN PEDIATRIC PATIENTS WITH ENDOCRINE DISEASES: EVIDENCE FROM A SYSTEMATIC REVIEW

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Abstract. Selenium (Se) is essential micronutrient involved in several physiological processes. In many regions around the world, a suboptimal intake of Se has been reported in several health conditions, also in pediatric age. Studies on association between Se level and diseases in children reported contrasting results. We took an aim to perform a systematic review of literature and provide evidence-based conclusion on the magnitude of Se deficit in endocrine diseases in children. PubMed, ISI WoS, and Scopus databases were searched to identify eligible studies, published until July 25, 2019. Methodological quality was assessed using Newcastle–Ottawa Scale. After careful selection, 13 eligible studies were included. Majority were conducted in Turkey (n=5) and Iran (n=5), and sample size varied from 61 to 628 children, with a mean (±SD) age of cases from 5.1±1.6 months up to 13.8±4.5 years. Eleven studies focused on different thyroid diseases, and two on children with type 1 diabetes mellitus (T1DM). In goitrous patients, Se level ranged from mean (±SD), 25.7±20.68 μg/L to 114.9±34.1 μg/L, while in patients with T1DM was 20.9±12.9 μg/mL and mean (95% CI)=58.4 μg/L (55.0–63.09). We may conclude that goiter and thyroid dysfunction are prominent signs of Se deficiency in children. Although deficiency of iodine and selenium are usually combined in some area, our systematic review showed that Se deficiency is important goitrogenic factor in school children. Further randomized controlled trials are needed to adequately explore the role of Se in endocrine disorders in children, across different populations and regions.

Key words: Selenium, endocrine, thyroid, diabetes, pediatric, systematic review.

Introduction

Selenium (Se) is a trace mineral and one of the essential micronutrients involved in several physiological processes [1]. It is a constituent of selenoproteins many of which are engaged in protection against oxidative stress [2], and a cofactor of many enzymes involved in several major metabolic pathways [3–6]. It is involved in thyroid metabolism as a cofactor of the glutathione peroxidase (GPx), protecting the thyroid gland against oxidative stress, and iodothyronin deiodinase enzymes, converting thyroxine (T4) to triiodothyronine (T3) [4, 6–9]. Being so important in human organism, the deficiency of Se can endanger human health and lead to misbalance of many biochemical processes further resulting in disease [10, 11].

Se intake and its level in the body depend on the person’s diet, where major sources of Se intake are plant foods, meat and meat products, nuts (Brazil nuts), cereals, fish and shellfish [12, 13]. In many regions around the world, people are exposed to inadequate content of Se in food because of the low Se content in the soils where plants and animals are grown [6, 14, 15]. Activity of Se-dependent thyroid enzymes, in case of Se deficiency, could cause impairment of the thyroid metabolism even in the situation of adequate iodine intake [16]. Also, deficit of Se has been associated with the poor immune response [17, 18]. In general, association of Se deficiency with many diseases has been documented, among which the increased risk of thyroid cancer, infections and immunodepression, diabetes, Keshan’s disease and endemic myxedema cretinism, mostly suggested to be due to the lack of protection against the oxidative stress [15, 19, 20].

Suboptimal intake of Se has been reported in several health conditions also in the pediatric age [21]. In Hashimoto’s thyroiditis in childhood, the deficiency of Se may promote initiation or progression of the disease [17, 22, 23]. Also, in other conditions of thyroid dysfunction in children, congenital hypothyroidism and goiter, different levels of serum Se have been demonstrated among cases and controls [16, 24]. Lower levels of Se and consequent oxidative damage are one of the possible factors involved in the etiology of diabetes mellitus in children [25]. Lower Se levels have also been reported in children with iron-deficiency anemia, dilated cardiomyopathy and acute lymphoblastic leukemia, when compared to the matched healthy controls [26, 27]. Low selenium levels also affected early neonatal morbidity in premature infants [28], and has been associated with hypoxia and respiratory diseases [29].

Studies on the association between Se level and diseases in children reported significantly lower levels of
Se in cases or no difference between levels in cases and controls. Since endocrine health and hormonal balance are of great importance, particularly in the childhood, for normal growth and development, we took an aim to perform a comprehensive and systematic review of the literature in order to provide a general overview and draw evidence-based conclusion on the prevalence and magnitude of the Se deficit in endocrine diseases in children.

Material and Methods

Literature Search Strategy

In order to retrieve primary studies, a systematic bibliographic search was conducted in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [30] through a multi-engine search of PubMed, ISI Web of Science (WoS), and Scopus databases. For initial search of the PubMed database, the following combination of subject headings and text words was used: (((selenium OR selenate OR “selenium derivative” OR “selenium compound” OR “antioxidant cocktail” OR selenite OR “sodium selenite” OR selenomethionine OR selenocysteine OR ebselen OR “selenious acid” OR “selenium-binding protein” OR “trace element” AND (lack OR deficit OR deficiency OR reduction OR shortage OR decreas* OR insufficien*)) AND (pediatric* OR child OR preschool OR school OR infan* OR adolescen* OR young*))). The remaining two databases were searched using appropriately modified PubMed query (detailed search queries are available upon request). Our search was restricted to studies conducted on humans and published up until July 25, 2019 in English, Italian or Serbian language.

Study Selection

Records from three different electronic databases were retrieved and cross-linking was performed in order to remove duplicates. Titles and abstracts of the identified records were screened and full texts of the initially eligible articles were obtained and evaluated for final eligibility. All of the steps are documented in the PRISMA flow diagram.

Studies were considered eligible if they met the following inclusion criteria: cross-sectional, case-control or cohort study design; studies on children or adolescents ≤18 years old with endocrine disease; studies that evaluated serum/plasma levels of selenium. Other reviews, letters, commentaries, editorials, case studies, studies conducted on cell or animal model were further excluded. Justification for the exclusion of records was specified and any disagreement in opinion between reviewers was resolved through discussion.

Data Extraction, Synthesis and Quality Assessment

Extraction of the data from each eligible study was conducted and data was entered into standard Excel form in order to synthesize and present the results. Data on first author’s name, year of study publication, country where the study was conducted, type of study design, type of endocrine disorder, total number of children, their age, percent of male participants, number of cases/controls, Se source (plasma or serum), measurement method of Se, measured concentration of Se (in cases/controls), reported statistical findings (if available). Due to the absence of common statistical estimates of effect in the included studies, we were unable to perform a quantitative pooling of data through meta-analysis thus we used a narrative synthesis to describe the findings.

Methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) for case-controls studies [31] and the adapted version by Herzog et al. [32] for the cross-sectional studies. Three main perspectives of the methodological quality of each included study were evaluated: selection of the study groups; comparability of the groups; and the ascertainment of outcome and exposure for cross-sectional and case-control studies, respectively. This tool uses a star system to assign a maximum of nine stars for case-control and ten for cross-sectional studies, across the evaluated domains. Studies were classified as good (≥6 stars), moderate (3-5 stars) and low (<3 stars) quality based on the maximum score. Detailed instructions for using this tool are provided elsewhere [33].

Results

Literature Search and Study Selection

A total of 4272 records were identified through the search of PubMed, ISI WoS and Scopus databases. After removing duplicates, 3312 titles and abstracts were screened, leading to a careful selection of 239 full text articles to be assessed for further eligibility. Of these, 226 articles were excluded for not meeting the inclusion criteria, leaving 13 eligible studies to be included in the qualitative synthesis [34, 35, 44–46, 36–43]. Detailed process of literature search and study selection is presented in Figure 1.

Characteristics of the Studies

Majority of the included studies were conducted in Turkey (n=5) and Iran (n=5), and by one in Poland, Ethiopia and Democratic Republic of the Congo (Table 1). Publication years ranged from 1990 [46] to the most recent one from 2018 [44]. Most of the studies used cross-sectional study design [34–41] while the remaining five were case-control studies [42–46]. Sample size varied from 61 [43] to 628 children [38] with mean age of cases spanning from 5.1±1.6 months [44] to 13.8±4.5 years [43]. Percentage of boys was different across the included studies, with a minimum of 21.95% [42] to a maximum of 71.25% [46]. Considering the investigated endocrinological disease, 11 studies focused on different thyroid disorders, namely goiter [34–41] and hypo-
thyroidisms [42,44], while the remaining two explored selenium status in children with the type 1 diabetes mellitus (T1DM) [43, 45]. Number of cases ranged from 48 [35, 39] to 280 [38] goitrous, and 35 [43] to 87 [45] children with T1DM.

Details on the selenium concentrations and main findings from the included studies are summarized in Table 2. Atomic absorption spectrometry was the most widely used method to measure the level of Se in serum [34–38, 42, 44, 46] and plasma [39–41, 43, 45]. Mean concentration of Se was different across the investigated populations and diseases. For goitrous patients, Se levels ranged from 25.71±20.68 μg/L [34] to 114.9±34.1 μg/L [36], while in patients with T1DM were 20.9±12.9 μg/mL [43] and 58.4 μg/L [45].

In general, level of Se was lower in children with goiter [35, 36, 39, 41] and in children with T1DM [43] or there was no difference reported between cases and controls in children with goiter and Hashimoto thyroiditis [38, 42]. Studies that had investigated correlation of Se level and several clinical parameters reported different findings, negative [34, 41], positive [39, 42], mixed [38, 44] some positive and some negative, and no significant correlation [35, 37, 40] in thyroid patients. In particular, a study by Gashu and colleagues reported that serum Se was negatively associated with T4, but positively with T3 concentration, and that a unit increase in concentration of Se could increase the serum T3 concentration by a factor of 0.16 [38]. On the other hand, Cinaz et al. demonstrated the lack of correlation between serum Se levels and thyroid function tests in their study [35]. In two studies conducted on diabetic patients, a negative correlation was reported between Se level and glycosylated hemoglobin (HbA1c) level [43], while Salmonowicz et al. reported non-significant correlations across different parameters [45]. Overall, the body of evidence in our review was characterized by a moderate to high quality level. Methodological quality of the included studies was good, especially of those cross-sectional study design, where two studies [34, 38] scored maximum stars across all evaluated domains. Case-control studies were mostly of moderate to good methodological quality (Table 3).

Fig. 1 Flowchart depicting literature search and study selection process
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Endocrine disease</th>
<th>Total number of children</th>
<th>Age range, mean±SD (years)</th>
<th>Males, n (%)</th>
<th>Number (n) of cases and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aydin, 2002 [34]</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>73</td>
<td>Range=7-12; mean±SD=9.56±1.77</td>
<td>35 (48%)</td>
<td>Cases (56); controls (17)</td>
</tr>
<tr>
<td>Cinaz, 2004 [35]</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>165</td>
<td>Mean±SD=9.04±1.91</td>
<td>NR</td>
<td>Cases (48); controls (117)</td>
</tr>
<tr>
<td>Dabbaghmanesh, 2007 [36]</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>500</td>
<td>Range=8-15</td>
<td>NR</td>
<td>Cases (198); controls (302)</td>
</tr>
<tr>
<td>Erdogan, 2001 [37]</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>Goiter (endemic)</td>
<td>251</td>
<td>Range=9–11</td>
<td>123 (49.01%)</td>
<td>Children from cities: Ankara (62), Kastamonu (59), Bayburt (59), and Kastamonu (66)</td>
</tr>
<tr>
<td>Gashu, 2016 [38]</td>
<td>Ethiopia</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>628</td>
<td>Range=4.5–5; mean±SD=4.74±0.15</td>
<td>311 (49.52%)</td>
<td>Cases (280); controls (348)</td>
</tr>
<tr>
<td>Giray, 2001 [39]</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>121</td>
<td>Range=15–18</td>
<td>52 (42.98%)</td>
<td>Cases (48); controls in-region controls (49), and out-region (24)</td>
</tr>
<tr>
<td>Hashemipour, 2008 [40]</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>219</td>
<td>Range=7-13; mean±SD=9.3±1.0</td>
<td>101 (46.12%)</td>
<td>Cases (108); controls (111)</td>
</tr>
<tr>
<td>Keshteli, 2009 [41]</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>Goiter</td>
<td>168</td>
<td>Range=6-13; mean±SD=9.39±1.18 (girls) and 9.47±1.12 (boys)</td>
<td>71 (42.26%)</td>
<td>Case (96); controls (72)</td>
</tr>
<tr>
<td>Nourbakhsh, 2015 [42]</td>
<td>Iran</td>
<td>Cross-control</td>
<td>Hashimoto’s thyroiditis and hypothyroidism</td>
<td>82</td>
<td>Children with Hashimoto’s thyroiditis, mean±SD=13.0±4.2; with hypothyroidism, mean±SD=11.4±3.3; controls, mean±SD=12.4±3.0</td>
<td>18 (21.95%)</td>
<td>Cases: Hashimoto’s thyroiditis (35), hypothyroidism (22); and controls (30)</td>
</tr>
<tr>
<td>Ozenc, 2015 [43]</td>
<td>Turkey</td>
<td>Cross-control</td>
<td>Type 1 diabetes mellitus (T1DM)</td>
<td>61</td>
<td>Cases, mean±SD=13.8±4.5; controls, mean±SD=12.8±3.3</td>
<td>34 (55.74%)</td>
<td>Cases (35); controls (26)</td>
</tr>
<tr>
<td>Rostami, 2018 [44]</td>
<td>Iran</td>
<td>Cross-control</td>
<td>Congenital hypothyroidism</td>
<td>99</td>
<td>Cases, range=0.25–1; mean±SD=0.42±0.13; controls, range=0.08–1.25, mean±SD=0.52±0.12</td>
<td>49 (49.50%)</td>
<td>Cases (39); controls (60)</td>
</tr>
<tr>
<td>Salmonowicz, 2014 [45]</td>
<td>Poland</td>
<td>Cross-control</td>
<td>Type 1 diabetes mellitus (T1DM)</td>
<td>155</td>
<td>Children with T1DM range=2–19, mean±SD=13.0±4.0; siblings range=4.5–16.5, mean±SD=13.2±3.7; and control groups range=10.5–18, mean±SD=14.8±2.2</td>
<td>79 (50.97%)</td>
<td>Cases (87); controls: siblings of the patients with T1DM (27 children) and healthy (41) children</td>
</tr>
<tr>
<td>Vanderpas, 1990 [46]</td>
<td>Republic of Zaire (Democratic Republic of the Congo)</td>
<td>Cross-control</td>
<td>Endemic myxedematous cretinism</td>
<td>80</td>
<td>Cases, range=3–25; controls, range=9-18</td>
<td>57 (71.25%)</td>
<td>Cases (28); controls (52)</td>
</tr>
</tbody>
</table>
### Table 2 Selenium concentrations and main findings from the included studies

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Biological sample for selenium measurement</th>
<th>Measurement method for selenium concentration</th>
<th>Selenium concentrations in cases and controls</th>
<th>Reported correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aydin, 2002 [34]</td>
<td>Serum</td>
<td>Atomic absorption spectrometry</td>
<td>Goitrous, mean±SD= 25.71±20.68 ng/mL; non-goitrous, mean±SD= 47.76±22.84 ng/mL</td>
<td>Negative correlation was reported between thyroid volume and Se level (r=0.32, p&lt;0.05)</td>
</tr>
<tr>
<td>Cinaz, 2004 [35]</td>
<td>Serum</td>
<td>Spectrophotometer (Unicam 959 AA)</td>
<td>Goitrous, mean±SD= 52.39±10.87 ng/mL; non-goitrous, mean±SD= 58.94±15.42 ng/mL; p=0.002</td>
<td>Serum Se levels did not correlate with the thyroid function tests, and T3, T4, and TSH levels are found to be similar in goitrous and nongoitrous children.</td>
</tr>
<tr>
<td>Dabbaghmanesh, 2007 [36]</td>
<td>Serum</td>
<td>Atomic absorption spectrometry (Chemtech Analytical CTA 2000, AAS)</td>
<td>Goitrous, mean±SD= 114.9±34.1 ng/mL; non-goitrous, mean±SD= 121.9±28.7 ng/mL; p&lt;0.05</td>
<td>NR</td>
</tr>
<tr>
<td>Erdogan, 2001 [37]</td>
<td>Serum</td>
<td>Atomic absorption spectrometer (Hitachi Z-8200® polarized Zeaman)</td>
<td>Study area: Ankara, mean±SD= 54.82±15.73 nmol/L; Kastamonu, mean±SD= 50.9±13.38 nmol/L; Bayburt, mean±SD= 57.54±14.60 ng/mL; and Trabzon, mean±SD= 52.22±14.30 ng/mL</td>
<td>No significant correlations between serum Se concentrations and studied parameters (i.e., Thyroid volume, thyiocyanate (SCN−) overload, thyroid hormones, sensitive TSH (sTSH) levels, and urinary iodine concentrations (UICs)) was detected.</td>
</tr>
<tr>
<td>Gashu, 2016 [38]</td>
<td>Serum</td>
<td>Mass spectrometer (PerkinElmer, ELAN9000, Norwalk, CT, USA)</td>
<td>NR (mean Se concentrations of goitrous and nongoitrous children were not significantly different, p&gt;0.05). Entire study population, median=61.4 μg/L, range=10.7-290.9 μg/L</td>
<td>Serum Se was negatively correlated to T4 concentration (r=−0.22, p=0.01).</td>
</tr>
<tr>
<td>Giray, 2001 [39]</td>
<td>Plasma</td>
<td>Spectrofluorometric method</td>
<td>Total goiter group, mean±SD= 67.1±10.9 μg/L; total in-region control, mean±SD= 75.0±14.6 μg/L; and out-region control group, mean±SD= 75.3±12.8 μg/L</td>
<td>In “all severely deficient children” a positive correlations of urinary iodine and Se were observed (r = 0.42, p&lt;0.05).</td>
</tr>
<tr>
<td>Hashemipour, 2008 [40]</td>
<td>Plasma</td>
<td>Atomic absorption spectrometer</td>
<td>Goitrous, mean±SD= 62.7 g/L; non-goitrous, mean±SD= 60.8 g/L; p = 0.42</td>
<td>No correlation was found between serum Se concentration and baseline data of the patients including height, weight, BMI and age.</td>
</tr>
<tr>
<td>Keshteli, 2009 [41]</td>
<td>Plasma</td>
<td>Atomic absorption spectrometer</td>
<td>Goitrous, mean±SD= 66.86±21.82 μg/L; non-goitrous children, mean±SD= 76.67±23.33 μg/L; p=0.006</td>
<td>In goitrous children, Se level was reversely correlated with age (r=−0.24, p=0.02), BMI (r=−0.20, p=0.05) and body surface area (r=−0.26, p=0.01) and was positively correlated with T4 (r=0.22, p=0.03).</td>
</tr>
<tr>
<td>Nourbakhsh, 2015 [42]</td>
<td>Serum</td>
<td>Atomic absorption spectrometer (ContraAA 700, Analytik Jena AG, Jena, Germany)</td>
<td>Hashimoto’s thyroiditis, mean±SD= 91.6±17 μg/L; hypothyroidism, mean±SD= 85.9±14.8 μg/L; controls, mean±SD= 97.2±29.4 μg/L</td>
<td>Se levels did not show any significant correlation with glutathione peroxidase but it had a significant correlation with selenoprotein P (r=0.34, p&lt;0.02)</td>
</tr>
<tr>
<td>Ozenc, 2015 [43]</td>
<td>Plasma</td>
<td>Atomic absorption spectrophotometry (Vrian Techtron Pty, Ltd., Victoria, Australia)</td>
<td>T1DM, mean±SD= 20.9±12.9 μg/mL; controls, mean±SD=32.6±10.2 μg/mL</td>
<td>There was a negative correlation between Se and HbA1c levels (r=−0.44, p=0.01)</td>
</tr>
<tr>
<td>Rostami, 2018 [44]</td>
<td>Serum</td>
<td>Atomic absorption spectroscopy</td>
<td>Hypothyroidism, mean±SD= 10.5±0.65 mg/L; controls, mean±SD=55.17±8.55 mg/L; p = 0.01</td>
<td>No statistically significant correlations were found between Se concentration and TSH level (r = 0.13, p = 0.29), and FT4 concentration (r = 0.07, p = 0.54). There was a significant correlation between prooxidant-antioxidant balance (PAB) value and serum Se concentration, and also between Se concentration and MCV (for all parameters, p&lt;0.05)</td>
</tr>
<tr>
<td>Salmonowicz, 2014 [45]</td>
<td>Plasma</td>
<td>Atomic absorption spectrophotometer (SOLAAR M6, Thermo Elemental, Great Britain)</td>
<td>Patients with T1DM, mean (95% CI)= 58.4 μg/L (55.0–63.9); siblings of patients with T1DM, mean (95% CI)=53.45 μg/L (46.09–65.21); healthy controls, mean (95% CI)= 53.3 μg/L (45.78–70.17)</td>
<td>In patients with T1DM no significant correlations were found between Se and HbA1c (r=0.2, p=0.07), age (r=0.01, p = 0.89), TG (r = −0.05, p = 0.72), TG (r = −0.07, r = 0.59), HDL-C (r = −0.12, p=0.45), LDL-C (r = −0.02, p = 0.89), TCHDL-C (r = 0.20, p = 0.22)</td>
</tr>
<tr>
<td>Vanderpas, 1990 [46]</td>
<td>Serum</td>
<td>Spectrofluorimetry</td>
<td>Cases, mean±SD= 443 ± 188 nmol/L; controls, mean±SD=343 ± 176 nmol/L; p&lt;0.1</td>
<td>NR</td>
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</tbody>
</table>

NR= not reported; SD=standard deviation; T1DM=Type 1 diabetes mellitus
**Table 3** Methodological quality of the included studies

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/Exposure</th>
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<tbody>
<tr>
<td>Aydin, 2002 [34]</td>
<td>CS</td>
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</table>

CS = cross-sectional; CC = case-control.

Note: A study can be awarded a maximum of four stars for case-controls and five stars for cross-sectional study within the selection category. A maximum of two stars can be given for comparability and three stars for outcome/exposure categories.

**Discussion**

Although discovered more than two centuries ago, Se and its role in health and disease remained underestimated and not fully elucidated. Endemic deficiency in large areas of central Asia clearly demonstrated its critical importance for survival. There are two well established entities of selenopenia: Kashin-Beck osteochondropathy and Keshan disease, a severe cardiomyopathy characterized by fulminant heart failure [47, 48]. The later mainly affects young children and women in childbearing age and it is apparent in population with particularly low Se intake (<15 μg/d), in some areas of China. It is noteworthy to mention that there is a relatively narrow range of Se intake, between deficiency (<30 μg/d) and toxicity (>900 μg/d) [49]. Numerous beneficial effects are attributed to Se and are extensively investigated in adults: antioxidant effects, correct functioning of the immune system, antiviral effects (nowadays of special interest), decrease in the risk of miscarriage, effects on bone metabolism, regulation of normal spermatogenesis development and motility, beneficial effect on mood [6, 47, 50, 51]. Interventional studies with Se in different pathological conditions in pediatric age are very rare.

In the current review, we selected 13 articles with the aim to investigate interdependence of Se levels and clinical presentation of endocrine diseases in children and adolescents. Majority of them refers to thyroid disorders and thyromegaly. Only two were performed in children with T1DM. It is expected finding taking into account that thyroid represents the organ which is most abundant in Se per gram of tissue, even richer than the brain, due to a high content of selenoproteins [6]. According to these data, the most frequent and severe Se deficiency is present in some parts of Africa (Northern Zair and Ethiopia) and Asia (China, Iran and Turkey) [38, 46, 49]. In a cross-sectional study on 628 children from Gonder, town of the Amhara region of Ethiopia, a goiter was found in 44.6% of them. The majority of children (88.6%) had suboptimal iodine supply (<100 μg/l). The presence of Se deficiency (serum Se <70 μg/l) was recognized as a problem in 57.8% of children [38]. Also, serum Se was negatively associated with T4 level in young children from this region. Vanderpas et al. emphasized that combined iodine and Se deficiency could be associated with the elevated frequency of myxedematous cretinism as a consequence of thyroid involution [46]. Similarly to observations from China, the distribution of Se deficiency was highly variable such that the deficiency and toxicity occurred in populations living just about 20 km apart, depending strongly on the geochemical characteristics of the soil in these specific areas [46, 49].

As mentioned above, in some severely iodine-deficient areas a concomitant deficiency of Se aggravates hypothyroidism leading to the myxedematous cretinism [14, 46]. On the other hand, an adequate selenium supply protects the thyroid from damage due to excessive iodine exposure, thus a selenium deficit should be corrected before the introduction of iodine supplementation when both deficits coexist [14, 52, 53]. Selenium deficiency was negatively associated with serum T4, but almost all children had normal level of T3. Vanderpas et al. suggested that in iodine-deficient subjects, Se deficiency may help maintaining the T3 concentration at normal level [46]. We find that it is just opposite from what could be expected, taking into account the role of Se containing deiodinase DIO1 in conversion of T4 to T3. Improved peripheral deiodination of T4 should provide increase in T3/T4 ratio that is confirmed after Se supplementation in school children from Se deficient area, evident from the study of Contempre et al. [54]. From 11 studies concerning the interdependence of Se level and thyroid status, two demonstrated a positive correlation, one to T4 and another to T3. In the study of Gashu et al., Se concentration was negatively associated with T4 level in young children from this region. Vanderpas et al. suggested that in iodine-deficient subjects, Se deficiency may help maintaining the T3 concentration at normal level [46]. We find that it is just opposite from what could be expected, taking into account the role of Se containing deiodinase DIO1 in conversion of T4 to T3. Improved peripheral deiodination of T4 should provide increase in T3/T4 ratio that is confirmed after Se supplementation in school children from Se deficient area, evident from the study of Contempre et al. [54]. 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some high-altitude mountain villages. Iodization of salt was introduced in Turkey in 1968, but IDD (Iodine De
ciency Disorders) are far from eradication in this country [39]. For comparison, iodization of salt in former
Yugoslavia started in 1956 and then reevaluated and reinforced in 1993, when the amount of iodine was dou-
bled [55]. Giray et al. evaluated Se concentrations in
goitrous children with severely and moderately iodine
deficiency in comparison with normal and mildly iodine
deficient non goitrous children serving as control, and
found signiﬁcantly lower Se values in the goitrous
group. The same study showed lower level of antiox-
idant blood enzymes glutathione peroxidase, catalase
and superoxide dismutase, suggesting alterations in antiox-
diant defense system and multiple micronutrient
deficiency [39]. All Turkish studies reported high goiter
persistance, despite normalization of the iodine status.
Goitrous children from Turkey had moderate to severe
Se deﬁciency in iodine depleted as well as in the iodine
repleted areas [34, 39]. Similar to Turkish experience,
the Iranian studies in former endemic areas showed high
percentage of goiter in school children. The deﬁciency
of both trace elements, iodine and selenium is even
more severe than what was reported in Turkey. The
most affected endocrine gland by Se deﬁciency was
thyroid. Studies from Turkey, as well as from Iran re-
ferred goiter in children as the most prominent clinical
sign of selenopenia (9 out of 11 studies). Unfortunately,
even in the cross-sectional studies, Se level was not
measured in the whole group, but only in goitrous chil-
dren, selected by palpation of the gland when some se-
verely Se deﬁcient children might be omitted. In select-
ed children with thyromegaly the widest difference in
Se level between goitrous and non-goitrous children
was found in the study of Aydin et al., 25.71 μg/L and
47.76 μg/L, respectively [34]. The authors found signif-
icant negative correlation between thyroid volume and
Se levels. On the other side, Gashu [38] and Hashemi-
pour [40] did not ﬁnd signiﬁcant difference in Se levels
between goitrous and non-goitrous children. Obviously,
the role of other goitrogens in food or another trace-
element deﬁciency should be additionally evaluated.

Extremely low Se level was found by Rostami et al.
in the group of hypothyroid children [44]. Only one
pediatric study from Iran, among selected in our review,
referred to autoimmune thyroid disease. It failed to ﬁnd
signiﬁcant difference in Se levels between patients with
Hashimoto’s thyroiditis and normal controls [42]. It is
expected that having a normal Se level provides ef-
ective thyroid function and diminishes oxidative stress in
thyroid cells, thus protecting thyroid from autoimmu-
nity. In adult patients with chronic autoimmune thyroiditis
from Germany and Greece, a Se supplementation de-
creased thyroid peroxidase antibodies [56, 57]. A strik-
ing majority of these patients reported an improvement
in mood and well-being after 6 months of combined
treatment (LT4+Se) [57]. In children, this effect was not
conﬁrmed [42]. However, a recent meta-analysis did not
present sufﬁcient data on clinical efﬁcacy of selenium
supplementation in chronic autoimmune thyroiditis in
adults, and the authors concluded that further investiga-
tions are warranted [51].

Only two studies on children with T1DM were in-
cluded as eligible in our systematic review [43, 45].
Hyperglycemia in diabetes increases or potentiates the
oxidative stress. In the Turkish study a signiﬁcantly
lower levels of Se were found in diabetic children in
comparison with controls and it correlated negatively with
the HbA1c. Expectantly, the level of Se-containing
enzyme, GPx was signiﬁcantly higher in diabetic chil-
dren [43]. We may explain this ﬁnding by enhanced the
need for GPx antioxidant activity that consumes more
Se in diabetic subjects. In the study of Polish authors, on
a larger group of patients, difference in the GPx activity
between diabetic children and non-diabetic controls was
not conﬁrmed [45]. It would be of interest to determine
and to compare Se levels in different stages of diabetes
in children (prediabetes, at admission, in acute metabol-
ic decompensation, remission period, permanent stable
or brittle diabetes). These results could be of immense
practical importance for the prevention strategies.

Strengths and Limitations

To the best of our knowledge, this is the ﬁrst review about
the selenium deﬁciency in endocrine diseases to focus
speciﬁcally on pediatric population, and thus has several
strengths. First, we used a comprehensive methodological
approach and careful selection of the studies, and also did
an extensive data extraction from the included studies
and provided a synthesis of evidence on this issue. Sec-
ond, our search covered wide time interval and several
different populations of children across different regions
and countries. Further, the methodological quality of
included studies was of moderate to high level, which
was conﬁrmed by a critical evaluation of their study
design using appropriate evaluation scale.

However, there are some limitations that should be
considered when interpreting our results. We only
searched for published studies in English, Italian and
Serbian language, thus we cannot exclude the possibility
of publication bias and also, this might have affected the
geographical representation of the studies. We did not
limit our search to any particular endocrine disease
since we wanted to present the general overview of the
Se levels in endocrine disorders in children, available so
far. Observational nature of the included studies is an-
other limitation that should be acknowledged. Further
randomized controlled trials are needed to adequately
explore the role of Se in disorders of the endocrine sys-
tem.

We were unable to perform a quantitative pooling of
the data through a meta-analysis due to the lack of effect
estimates in the included studies. Additionally, most of
the included studies investigated populations from low
and middle income countries thus our ﬁndings might
not be widely applicable to other populations, particu-
larly those from high-income countries, due to the pos-
sible difference in life-style, habits and particularly in diet. In fact, lack of information on dietary habits and Se intake from food as well as the genetic background of the participants might have influenced our findings, but these were not available to us since they were not explored in the included studies. This further underlines the need for more research in that direction. In particular, since the incidence of endocrine diseases, especially diabetes is rising across the world, a trans-regional multicenter studies on children to explore Se levels across different populations and regions are highly desirable.

Conclusions

We may conclude that thyroid disorders, goiter and thyroid dysfunction are prominent signs of Se deficiency in school children. Critical importance of thyroid function on early brain development, somatic growth and maturation, as well as for appropriate energy level for an active life, is impetus for further thorough investigation of selenostasis in wide population, especially in children and adolescents. For thyroid autoimmunity, there are insufficient data in the pediatric age. Although deficiency of iodine and selenium are usually combined in some area, our systematic review showed that Se deficiency is important goitrogenic factor in school children. Deficiency of other trace elements, like Zn (cofactor of TSH receptor) and iron (cofactor of thyroid peroxidase enzyme), necessary for appropriate thyroid function, should be further investigated.

The role of Se in autoimmunity is attractive and promising, but it is underinvestigated and its clinical use is not recommended routinely. Some selenopenic subjects with autoimmune diseases could have beneficial effects. Wider use of Se is not advised because of its potential toxic effects. High Se intake may lead to selenosis or increase risk of type 2 diabetes mellitus, glaucoma, cancer, cardiovascular mortality and peripheral arterial disease [6]. Thus, it is particularly important to ensure optimal and balanced diet, in both macro and micronutrients, for better metabolic health from an early age.

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References

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