Journal of Trace Elements in Medicine and Biology 50 (2018) 291–295

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Selenium inadequacy hampers thyroid response of young children after iodine repletion

Dawd Gashu[a,*], Grace S. Marquis[b], Karim Bougma[b], Barbara J. Stoecker[c]

[a] Center for Food Science and Nutrition, Addis Ababa University, Ethiopia
[b] School of Dietetics and Human Nutrition, McGill University, Canada
[c] Department of Nutritional Sciences, Oklahoma State University, USA

ARTICLE INFO

Keywords:
Selenium
Iodine
Thyroid metabolism
Thyroid hormones
Children

ABSTRACT

Selenium (Se) is an integral component of iodothyronine deiodinase, glutathione peroxidase and thioredoxin reductase enzymes and thus is important for normal thyroid function. This study investigated the influence of Se inadequacy on thyroid response of iodine-replete young children. Serum thyroxine (T_4), triiodothyronine (T_3), thyroglobulin (Tg), thyroid stimulating hormone (TSH), and Se were analyzed in 54–60 mo old children (n = 628) from the Amhara region of Ethiopia before salt iodization was commenced; analyses were repeated (n = 555) 15 mo after iodized salt became available. Iodized salt coverage increased from 12.2% to 91.6% of households. Median urinary iodine concentration (UIC) among children increased from 9 µg/l to 167 µg/l ($p < 0.001$). In addition, all thyroid indices except T_3 showed significant improvement ($p < 0.05$). Nearly, half of the study children (49.1%) had Se inadequacy (serum Se < 70 µg/l). Serum Se was significantly correlated with T_3 ($r = 0.38$, $p < 0.001$), T_4 ($r = 0.15$, $p < 0.001$), TSH ($r = -0.205$, $p < 0.001$) and Tg ($r = -0.11$, $p < 0.01$) concentrations 15 mo after iodine repletion; baseline serum Se and T_4($r = -0.22$, $p < 0.01$) were inversely correlated. Despite adequate iodine status, children with low serum Se had lower serum T_4 ($p = 0.003$) and T_3($p < 0.001$) but higher TSH concentration ($p = 0.003$). In the partial least square regression model, Se was among the latent variables significantly explaining T_4 and T_3. Results of the present study suggest that Se inadequacy negatively affects the thyroid metabolism of iodine-replete children and may present a substantial public health concern thus emphasize the need to consider correction of Se status for normal thyroid function as well as for benefits from its diverse biological roles.

1. Introduction

Selenium (Se) plays an important role in human physiology mainly through its presence in selenocysteine containing proteins. There are 25 human selenoproteins with diverse functions [1]; the iodothyronine deiodinases (IDIs), glutathione peroxidases (GPXs), and thioredoxin reductases (TRxRs) are among the selenoproteins with their function explicitly characterized [2]. Glutathione peroxidase 3(GPX3) provides antioxidant protection to thyrocytes from attack by hydrogen peroxide (H_2O_2) produced during thyroid hormone synthesis. In addition, IDI isoforms (D1, D2, and D3) play crucial roles in thyroid hormone synthesis, underlying the important relationship between Se nutrition and thyroid metabolism [3]. The IDI enzymes, D1 and D2 convert the biologically inactive T_4 to the bioactive T_3 (3, 5, 3′-triiodothyronine). In addition, D1 and D3 enzymes convert T_4 to the bioinactive rT3 (3, 5′, 3′-triiodothyronine [4].

The thyroid is among the glands or organs that retain the most Se per mass. Thus, it can maintain deiodinase activity even in a state of Se deficiency [5]. In addition, it is a priority organ in the hierarchy of Se supply [6]. However, results of several studies show that severe or extended Se deprivation reduces the IDI enzyme activity and alters thyroid metabolism even when iodine nutrition is adequate [7–14]. We previously reported Se deficiency as a public health problem in a severely iodine deficient area of the Amhara region, Ethiopia [15]. Compared to children with normal serum Se concentration, study children with Se inadequacy had significantly higher serum T_4 concentration suggesting a reduced activity of IDI enzymes converting T_4 to the biologically active T_3 [15]. The current study investigated the influence of Se status on the thyroid response of children, 15 mo after iodine repletion.

* Corresponding author at: Center for Food Science and Nutrition, Addis Ababa University, P. O. Box 1176, Ethiopia.
E-mail address: dawd.gashu@aau.edu.et (D. Gashu).

https://doi.org/10.1016/j.jtemb.2018.07.021
Received 31 January 2018; Received in revised form 21 July 2018; Accepted 23 July 2018

2. Materials and methods

2.1. Study participants

This study was conducted within a large cluster-randomized trial entitled 'Effect of Iodized Salt on Child Development in Amhara Region, Ethiopia'; a rural area characterized by the presence of moderate iodine deficiency [16]. The trial (NCT01349634) was registered with www.clinicaltrials.gov. Details of study site selection, sample size calculation, and recruitment of participants for the larger trial are reported elsewhere [15,17]. Briefly, 60 out of 75 districts from six zones of the Amhara region (West Gojjam, East Gojjam, South Gonder, North Wollo, South Wollo and Wagehmera) were randomly selected. From each of the 60 districts, one rural village was randomly selected. At baseline, all households with children aged 6–60 mo were registered and further categorized into 6–11 mo, 18-22mo, and 54–60 mo. The present study was nested within the larger study. A subset of 26 of the 60 districts were selected randomly and the analysis included only children from the 54–60 mo age group. Data for 624 children were analyzed at baseline; and 15 mo later samples from 555 of the children were available for analysis. The main study was a cluster randomized control trial in which the intervention districts received iodized salt approximately 4 mo earlier than it became available through normal market forces in the control districts. As the group difference in access to iodized salt was small and the thyroid markers indicated short-term iodine nutrition, the present study used a pre-post analysis approach to test the changes in thyroid profile of the children.

2.2. Blood collection and analysis

Protocols for blood collection, analysis and quality control were reported previously [15]. Briefly, blood was drawn by venipuncture into trace-element-free tubes, allowed to clot and centrifuged in the field. The serum was transported in vials to Bahir Dar in an icebox and kept at − 20 °C until transferred to the Ethiopian Public Health Institute (EPHI) at Addis Ababa and stored at −80 °C. Duplicates of frozen serum samples were shipped on dry ice to Oklahoma State University for Se analysis. Needles, blood tubes, vials, pipette tips and gloves recommended for trace mineral research were used throughout the work.

Serum Se was analyzed by Inductively Coupled Plasma Mass Spectrometer (PerkinElmer, ELAN9000, Norwalk, CT, USA) following dilution in 0.1% double distilled nitric acid (GFS Chemicals, Inc.). Calibrating standards were prepared by diluting a Se stock solution (Perkin Elmer Life and Analytical Sciences) in 0.1% nitric acid (GFS Chemicals, Inc.) and Triton- X 100 (Perkin Elmer Life and Analytical Sciences). Gallium was used as an internal standard. For quality control purposes, a serum trace elements certified reference sample (#66816, UTAK Laboratories, Inc; Valencia, CA) was analyzed at least every ten samples.The accuracy and precision of the method were 96% and 3.0%, respectively (certified value = 111 μg/l and the value obtained by the laboratory was 114.8 μg/l). Serum Se < 70 μg/l was used to define Se inadequacy [18].

An automated electro-chemilumenescense immuno assay using an Elecsys2010 clinical analyzer (Cobas e411, Roche Diagnostics GmbH, Mannheim, Germany) was used to analyze thyroid markers (T_4, T_3, TSH, and Tg) in serum. Elecsys reagents were used to calibrate the instrument every time thyroid markers were analyzed or new batches of reagents were used. Moreover, Preci Control Clin Chem Multi 1 and Preci Control Clin Chem Multi 2 reagents for each thyroid marker (T_3, T_4, TSH and Tg) were analyzed for quality control purpose and the readings were in the acceptable level. The laboratory was participating in the 'One World Accuracy' external quality assurance program.

2.3. Collection and analysis of urinary and salt iodine

Samples of table salt (approximately 10 g) were collected from the study households at both time points. Salt samples were assessed qualitatively on-site using a rapid test kit (RTK). The iodine content of salt samples found positive for the RTK were analyzed quantitatively by titration [19].

Spot urine samples for iodine analysis were collected into clean cups, and transferred to tubes. The tubes were wrapped in parafilm to avoid evaporation, transported in a cooled storage container, and kept at -20 °C at EPHI until analysis. Urinary iodine was determined by the colorimetric ceric ion arsenious acid wet ashing method based on the Sandell-Kolthoff reaction [19]. The detection limit of the instrument was 5 μg/l.

2.4. Statistical analysis

Descriptive statistics (proportions, mean, standard deviation, median, range) have been used to describe the data. The distribution of measured variables was tested using the Kolmogorov– Smirnov test. Non-normally distributed data were log-transformed for statistical tests that assume normality of data distribution. Pearson correlation to study the relationships between serum Se, iron status, and thyroid markers, and independent Student's *t*-test to compare thyroid markers by Se status were used. Predictor parameters displayed collinearity thus partial least squares (PLS) regression was used to identify parameters significantly predicting serum T_3 and T_4 concentrations. The predictor parameters tested in the model were UIC, T_3 (if T_4 was the response parameter), T_4 (if T_3 was the response parameter), TSH, Tg, ferritin, soluble transferrin receptor (sTFR), and Se concentration. SPSS for Windows (v18, Chicago, IL, USA) was used for statistical analyses and $p < 0.05$ was considered significant.

2.5. Ethical considerations

The study was approved by the National Health Research Ethics Review Committee at the Ethiopian Science and Technology Commission and the Institutional Review Boards at McGill University, Canada, and Oklahoma State University, USA. Written informed consent was obtained from all parents or guardians of the study children.

3. Result

The mean age of children at baseline was 56.9 ± 1.8 mo (54–60 mo) and 72.0 ± 1.9 mo (69–78 mo) at the second collection period. The iodized salt coverage increased from 12.2% to 91.6% of households. The median iodine concentration (by titration) of salt samples increased from below limit of detection during baseline to 14 ppm 15 mo after iodized salt became available. The median UIC after 15 mo of iodized salt availability was 167 μg/l (IQR 97, 287 μg/l) representing a substantial and clinically significant increase from baseline (9 μg/l; $p < 0.001$). Based on the WHO epidemiologic criteria for assessing iodine nutrition using median UIC, the study population had adequate iodine nutrition. However, despite the improvement, 26.4% of the study population had UIC classified as deficient (UIC < 100 μg/l) of whom 2.3% had UIC in the severely iodine deficient range (UIC < 20 μg/l), 7.1% had UIC in the moderately iodine deficient range (20–49 μg/l), and 17.0% had UIC in the mild iodine deficiency range (50–99 μg/l).

Compared to the cut-off for normal levels of thyroid markers, 2.9% of children had low serum T_3 (< 1.2 nmol/l), 2.7% had elevated serum Tg (> 78 μg/l), and 35.1% had elevated serum TSH concentration (> 4.2 mU/l). As expected, there was a significant change in the concentration of thyroid markers 15 mo after salt iodization (Table 1). However, there was a significant decrease in T_3 concentration in response to the consumption of iodized salt though it remained in the