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Assessment of the Selenium Status in Hypothyroid Children from North East of Iran

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ABSTRACT

Both iodine and selenium are essential important micronutrient required for the synthesis of thyroid hormones. The aims of this study are to assess selenium status in hypothyroid children and to determine its association with thyroid hormones metabolism. This cross-sectional study was conducted using a convenient sample of hypothyroid children attending to children endocrinology clinic between July 2015 and March 2016 in Neyshabur, Iran. Selenium, T4 and TSH in serum of 23 hypothyroid children, 1-72 month of age were measured. SPSS, version 11.5 was used to analyze the data. The Student´s t or the Mann-Whitney U and bivariate and partial correlation tests were used in the analyses. The mean age of the participants was 30 month (±25.09). The mean ± SD of plasma Selenium concentration in hypothyroid children was 98.79 ± 13.63 µg/l. Considering the conventional serum Selenium-deficiency cutoff (<90.0 µg/l), 26.08% of children had low serum selenium. Using the arbitrary level of thyroid hormones for normal thyroid metabolism, 17.39% of the children had elevated TSH level and 4.34% of the children had serum T4 < 4.7 nmol/l. Spearman correlation test showed that selenium level was significantly correlated with TSH (r= 0.63, p =0.001), weight (r= 0.53, p=0.008) and age(r=0.44, p=0.03). In study children, selenium level indicated reverse significant correlation with T4 (r=-.58, p=.004). In the present study, we showed that selenium deficiency plays a role in circulating thyroid hormones concentration and also affect the necessary levothyroxine dose required for hypothyroid children. These findings call for an increased attention to serum selenium levels in hypothyroid children. Selenium supplementation may be useful in hypothyroid treatment.

Key words: Hypothyroidism, Selenium, Thyroid hormones.

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1. INTRODUCTION

Congenital hypothyroidism (CH) is a common disease estimated to affect about 1 in every 3000-4000 births (1). Global program to control congenital hypothyroidism have considerable progress (2). Yet CH remains a major public health problem especially in low income countries. Thyroid hormones are essential for the development of critical organs including brain, lung and bone (3). Untreated CH will cause severe growth defect, neurological defects, hypotonia, bradycardia and other systemic impairment (4-6). Thyroid gland has the highest selenium concentration in human body (7). Selenium is an essential trace element in composition of selenoproteins synthesis. As yet, 25 selenoproteins are known and most of them are enzyme. The thyroid gland have high concentration of selenium because of high level of selenoenzymes, which are important for thyroid hormone metabolism. Both iodine and selenium are essential important micronutrient required for the synthesis of thyroid hormones. Deiodinases and glutathione peroxidases are the principle enzymes in the thyroid gland. Iodine is a main component of thyroid hormones thyroxine (T4) and triiodothyronine (T3). Selenium has two known role in thyroid function. First, it is a principle part of glutathione peroxidase, which acts as the cell antioxidant system to protect cells from free radicals. Second role for selenium is as a component of iodothyronine deiodinase enzyme. This enzyme converts the T4 to its biologically active form T3 and selenium is a principle part of selenocysteine which is essential for proper thyroid metabolism. As we know under normal circumstances, increasing in plasma T4 concentration results in suppressing pituitary gland axis and reduction in thyroid stimulating hormone (TSH). Under selenium deficiency,

the pituitary gland cannot recognize increased plasma TSH concentration and on the other hand the inhibition of deiodinase enzyme activity leads to reduction in T3 concentration. These mechanism have been documented in rodents but a possible interaction in humans is controversial and not tightly established (8, 9). A large epidemiological study in china reported a significantly higher risk of thyroid diseases in participants with low serum selenium (10). In another area, low serum selenium concentration was associated with thyroid enlargement (11). Human studies on the association of selenium with thyroid metabolism of children are limited. The serum selenium concentration differs in distinct regional population according to their race, geographical environment, eating habit and smoking. We did not find any study from our region looking at selenium status and its relationship with thyroid hormones in children. So that the purposes of this study are to assess selenium status in hypothyroid children and to determine its association with thyroid hormones metabolism.

2. MATERIALS AND METHODS

This cross-sectional study was conducted using a convenient sample of hypothyroid children attending to children endocrinology clinic between July 2015 and March 2016 in neyshabur, Iran. The purpose and method of the study were explained to parents and all those agreeing to participate in the study provided written informed consent. The study was approved by neyshabur university medical school ethics committee (First Protection Code of Human Subject in Medical Research). 23 hypothyroid children were examined for blood selenium level. All patients were receiving levothyroxine. Demographic information including age, sex, duration of the disease and weight were recorded in the check list. Exclusion criteria were other chronic disease, autoimmune disease, having seizure or mental retardation. Apart from these all patients were healthy and did not take any further medication, particularly no immunosuppressant or anti-inflammatory agents. Approximately 2 cc blood sample was collected from the antecubital vein of children by the clinical experienced nurses. The samples was placed in plastic tubes containing the anticoagulant EDTA-K2 and stored at -20 ^{o}C. Serum selenium concentration was analyzed by atomic absorption spectrophotometry Vryoni 240 Fs (USA) and arbitrary cut off for selenium deficiency was <90 micg/l by its manufactory. Thyroid function test including TSH, T4 and FT4 were measured fully automated chemiluminescent immunoassay Access 2 by Beckman and Coulter (USA). Reference intervals determined by the manufacturer were TSH: 1-7.2 micIU/ml, T4: 4.7-11micg/dl. Spss (version 11.5) was used to analyze the data. Qualitative variables are reported as number and percent among participants and the quantitative data as the mean ± standard deviation (SD). Comparison between means was done with the student´s t test or the Mann-Whitney U test after assessing the normality by using Shapiro-wilk test. The association between serum selenium and other variables was performed using bivariate and partial correlation test. In all calculations, P value < 0.05 was considered as statistically significant level.

3. RESULTS AND DISCUSSION

A total of 23 hypothyroid children were enrolled in this study. Of these, 14 (60.9%) were male. The mean age was 30 month (±25.09) with a range of 1 to 72 month. All 23 patients were treated with a mean levothyroxine dose of 4.83 + 3.98 µg/kg/dose. A summary of patients' characteristics is presented in Table 1.

Table 1. Participants characteristics, hypothyroid children, neyshabur, Iran, 2015-2016

	(mean ± SD) N= 23	Minimum – maximum
Age (month)	30 ± 25.09	1-72
Weight (kg)	12.43 ± 5.60	-
selenium (µg/l)	98.79 ± 13.63	75-127
Levothyroxine dose (mic/kg/dose)	4.83 + 3.98	1.25-20
Male (%) Female (%)	39.1 60.9	-

The mean ± SD of plasma Selenium concentration in hypothyroid children was 98.79 ± 13.63 µg/l. Selenium levels ranged from 75-127 µg/l. Considering the conventional serum Selenium-deficiency cutoff (<90.0 µg/l), 26.08% of children had low serum selenium. Table 2 shows thyroid hormones status in the study participants. Using the arbitrary level of thyroid hormones for normal thyroid metabolism, 17.39% of the children had elevated TSH level and 4.34% of the children had serum T4 < 4.7 nmol/l, whereas the majority of children had normal TSH and T4 as they are routinely treated by T4 substitution. Serum T4 and also selenium concentration did not differ by sex.

Table 2. Summary of thyroid hormones status in the study participants from the Neyshabur, Iran, July 2015 and March 2016

Thyroid hormones	(mean ± SD) N= 23	Normal value
TSH (mU/l)	5.89 + 8.29	1-7.2
T4 (nmol/l)	9.95 + 4.73	4.7-11

Spearman correlation test showed that selenium level was significantly correlated with TSH (r= 0.63, p = 0.001), weight (r= 0.53, p= 0.008) and age (r= 0.44, p= 0.03). In study children, selenium level indicated reverse significant correlation with T4 (r= -0.58, p= 0.004). Moreover, after controlling for TSH and weight, the correlation between selenium and T4 was still significant but the association became to some extent weaker (r= -0.46, p= 0.03). In addition, the patients who had higher serum selenium concentration, a lower dose of levothyroxine required (r= -0.20, p= 0.3). Correlation of serum selenium with T4, TSH, weight and levothyroxine receiving dose were indicated in Figure 1.

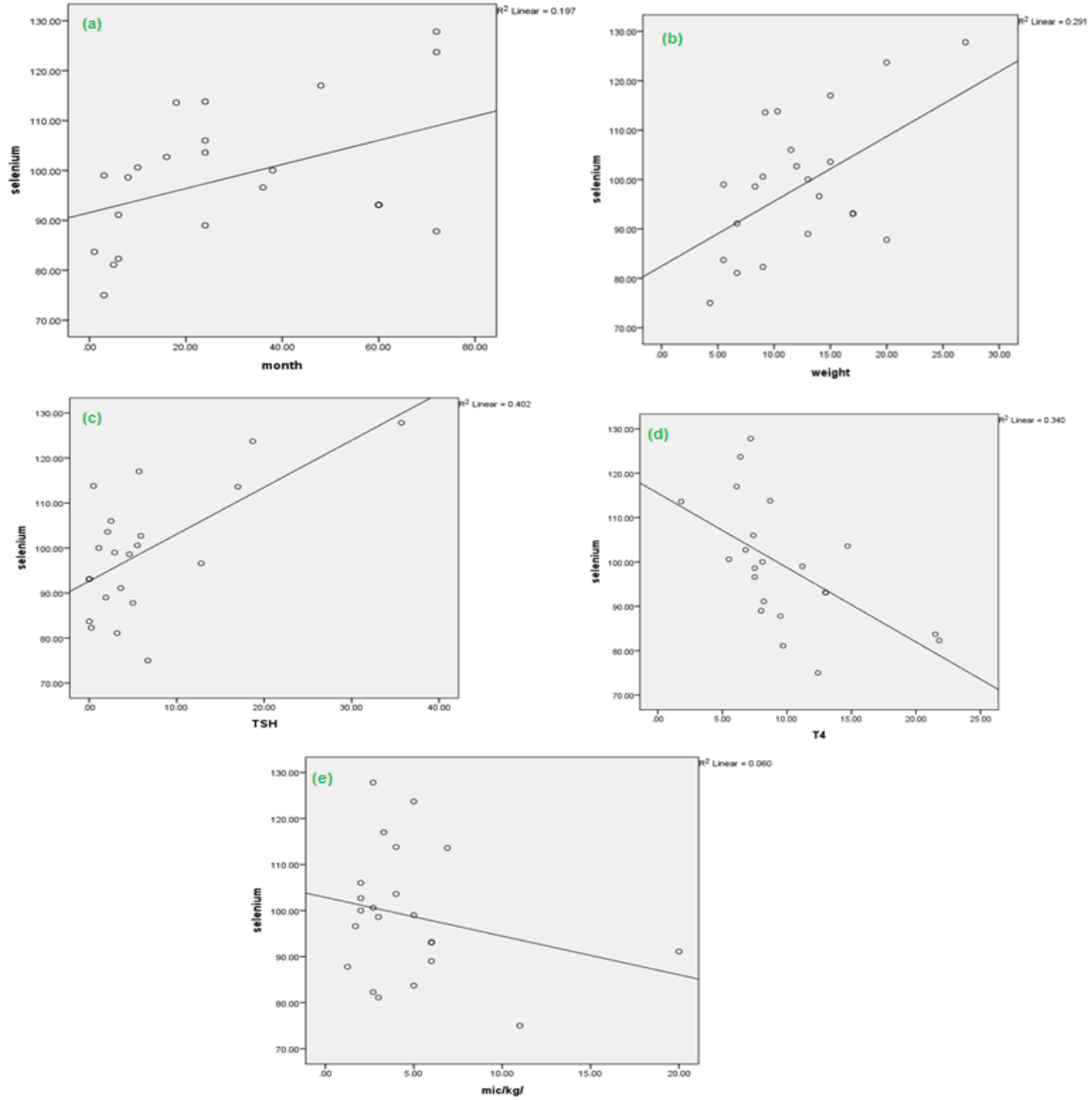

Figure 1. Spearman correlation of serum selenium concentration with a) age (month), b) weight, c) TSH, d) T4, e) levothyroxine receiving dose (mic/kg/dose)

This is the first study in our region to investigate the effect of serum selenium on thyroid feedback axis in the hypothyroid children. According to the present study the mean + SD of selenium level was 98.79 ± 13.63 and 26.08% of the hypothyroid children had low serum selenium level. The result of another study in central part of our country revealed that the prevalence of Selenium deficiency in goitrous children was 75.0% and their serum selenium level was 66.86±21.82 (12). In study from Ethiopia, highly selenium deficiency was found in children from the western part of the country but the children in eastern part had little or no selenium deficiency (13). Similar to these studies, the frequency of selenium deficiency and toxicity in china was highly variable in populations of just 20 km apart (14). Since the selenium level of the population is determined mainly by the food they consume. These variable distributions attributed to the selenium level in the soil, which varies by the geochemical characteristic (13). Based on several studies, there is a complex association between trace element selenium and thyroid hormone metabolism (15-17). Epidemiological studies indicated the association between moderate selenium deficiency and increased thyroid volume and thyroid nodularity and general risk of the other thyroid disease (10, 11, 18). Selenium is one of the trace elements with an important role in various biological functions and also it is the second essential trace elements for thyroid hormone production (19). Selenium modify thyroid axis by two mechanisms of antioxidation and deiodinase activity. In selenium deficiency, the activity of these two enzymes could be attenuated and thereby impair thyroid metabolism in both iodine deficient and non-iodine deficient patients (20). In our study, selenium level had strong and reverse correlation with serum T4. These findings were in

agreement with a recent study that low selenium level associated with higher concentration of plasma T4 (13, 21). In several studies in Iran (12, 22, 23), Turkey (24, 25) and Poland (26), goitrous patients had significant lower Selenium levels than nongoitrous ones. In two other studies, administration of selenium supplementation in children with severe selenium and moderate iodine deficiency and also severe selenium and severe iodine deficiency resulted a significant reduction in serum T4 concentration (27, 28). Sufficient selenium activates iodothyronine deiodinases type 1 and type 2 and increase the shift of T4 to T3. Thus, the strong contrary association between serum selenium and T4 concentration in this study indicated that selenium deficiency could prevent T4 to T3 conversion. Also in the present study we found significant direct association between selenium level and TSH, age and weight. Considering all of these factors, selenium was influential factor on T4 after controlling for TSH, age and weight. In rats, an increase in T4 concentration in response to low serum selenium level did not affect on pituitary-thyroid axis to release TSH (29). In contrast to the present study, Keshtli et al showed that selenium deficiency did not cause any significant dysfunction in thyroid hormone metabolism (12). In two other studies, results showed that the serum selenium concentration was not associated with TSH level (11, 30). Severe selenium or iodine deficiency can damage to the tryroid gland and cause myoedematous cretinism (16). Some studies have demonstrated that sever selenium and iodine deficiency can enlarged the thyroid volume and cause goiter (24, 31, 32). Selenium is also important for normal immune function. Selenium deficiency can cause impairment in both cell-mediated immunity and B-cell function (33, 34). In addition, selenoenzymes can reduce free radicals and act as an antioxidant. In WHO report, selenium deficiency can cause keshan disease that is a selenium responsive endemic cardiomyopathy that mainly affect children and woman in reproductive age (35). The coxsackie virus is specified as a pathogenic of Keshan disease. Main clinical manifestations of Keshan disase are congestive heart failure and cardiogenic shock. Selenium deficiency can increase the virulence of coxsackie virus and also help the conversion of a non-virulent strain to virulence. The major limitation of this study is that the study focused on selenium level and thyroid function at the same time, so this cross sectional does not have enough power to evaluate causal relationship. So a largo cohort or clinical trial to examine the effect of serum selenium level or selenium supplementation on thyroid axis, with larger patient numbers was recommended. In addition, classification of children according to their T4, TSH status is to some extent problematic. Thyroid function test (T4, TSH) is a relative indicator for thyroid metabolism. Serum tiroglobolin concentration, UIC and other micronutrients such as iron and cu (copper) are sensitive biomarker that has effect on thyroid hormone metabolism. We did not evaluate these parameters due to limited financial resource. However, the role of these parameters in thyroid metabolism should be measured in future study.

4. CONCLUSION

In the present study, we showed that selenium deficiency plays a role in circulating thyroid hormones concentration and also affect the necessary levothyroxine dose required for treatment of hypothyroid children. These findings call for an increased attention to serum selenium levels in hypothyroid children. Selenium supplementation may be useful in hypothyroid treatment.

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AUTHORS CONTRIBUTION

Author 1: Conception of the work, Data collection, Critical revision of the manuscript.
Author 2: Data collection, Critical revision of the paper.
Author 3: Design of the work, Data analysis, Drafting the manuscript, Final approval of the version to be published.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

REFERENCES

1. Jacob H, Peters C. Screening, diagnosis and management of congenital hypothyroidism: European Society for Paediatric Endocrinology Consensus Guideline. Archives of disease in childhood-Education & practice edition. 2015:edpract-2014-307738.
2. Zimmermann M. Iodine deficiency and excess in children: worldwide status in 2013. Endocrine Practice. 2013;19(5):839-46.
3. PORTERFIELD SP, HENDRICH CE. The role of thyroid hormones in prenatal and neonatal neurological development—current perspectives. Endocrine reviews. 1993;14(1):94-106.
4. Grüters A, Krude H. Detection and treatment of congenital hypothyroidism. Nature Reviews Endocrinology. 2012;8(2):104-13.
5. Larson CA. Congenital Hypothyroidism. Pediatric Endocrinology: Springer; 2013. p. 261-73.
6. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet journal of rare diseases. 2010;5(1):1.
7. Köhrle J. The trace element selenium and the thyroid gland. Biochimie. 1999;81(5):527-33.
8. Mittag J, Behrends T, Nordström K, Anselmo J, Vennström B, Schomburg L. Serum copper as a novel biomarker for resistance to thyroid hormone. Biochemical Journal. 2012;443(1):103-9.
9. Baltaci A, Mogulkoc R, Belviranli M. L-thyroxine-induced hyperthyroidism affects elements and zinc in rats. Bratislavske lekarske listy. 2012;114(3):125-8.
10. Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, Gao C, et al. Low population selenium status is associated with increased prevalence of thyroid disease. The Journal of Clinical Endocrinology & Metabolism. 2015;100(11):4037-47.
11. Rasmussen LB, Schomburg L, Köhrle J, Pedersen IB, Hollenbach B, Hög A, et al. Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. European Journal of Endocrinology. 2011;164(4):585-90.
12. Keshteli AH, Hashemipour M, Siavash M, Amini M. Selenium deficiency as a possible contributor of goiter in schoolchildren of Isfahan, Iran. Biological trace element research. 2009;129(1-3):70-7.

13. Gashu D, Stoecker B, Adish A, Haki G, Bougma K, Aboud F, et al. Association of serum selenium with thyroxin in severely iodine-deficient young children from the Amhara region of Ethiopia. European journal of clinical nutrition. 2016.
14. Fordyce F, Guangdi Z, Green K, Xinping L. Soil, grain and water chemistry in relation to human selenium-responsive diseases in Enshi District, China. Applied Geochemistry. 2000;15(1):117-32.
15. Duntas LH. Selenium and the thyroid: a close-knit connection. The Journal of Clinical Endocrinology & Metabolism. 2010;95(12):5180-8.
16. Kohrle J, Jakob F, Contempre B, Dumont JE. Selenium, the thyroid, and the endocrine system. Endocrine reviews. 2005;26(7):944-84.
17. Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. Nature Reviews Endocrinology. 2012;8(3):160-71.
18. Derumeaux H, Valeix P, Castetbon K, Bensimon M, Boutron-Ruault M-C, Arnaud J, et al. Association of selenium with thyroid volume and echostructure in 35-to 60-year-old French adults. European Journal of Endocrinology. 2003;148(3):309-15.
19. Hıncal F. Trace elements in growth: Iodine and selenium status of Turkish children. Journal of Trace Elements in Medicine and Biology. 2007;21:40-3.
20. Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. 2002;12(10):867-78.
21. Jochum F, Terwolbeck K, Meinhold H, Behne D, Menzel H, Lombeck I. Is there any health risk of low dietary selenium supply in PKU-children? Nutrition Research. 1999;19(3):349-60.
22. Brauer VF, Schweizer U, Köhrle J, Paschke R. Selenium and goiter prevalence in borderline iodine sufficiency. European journal of endocrinology. 2006;155(6):807-12.
23. Dabbaghmanesh MH, Sadegholvaad A, Ejtehadi F, Omrani G. Low serum selenium concentration as a possible factor for persistent goiter in Iranian school children. Biofactors. 2007;29(2-3):77-82.
24. Aydın K, Kendirci M, Kurtoğlu S, Karaküçük E, Kırış A. Iodine and selenium deficiency in school-children in an endemic goiter area in Turkey. Journal of Pediatric Endocrinology and Metabolism. 2002;15(7):1027-32.
25. Cinaz P, Karakas D, Camurdan M, Bideci A, Ayvali E, Yücel C. Goiter prevalence, serum selenium, and urine iodine status in a previously iodine-deficient area in Turkey. Biological trace element research. 2004;100(3):185-93.
26. Zagrodzki P, Szmigiel H, Ratajczak R, Szybinski Z, Zachwieja Z. The role of selenium in iodine metabolism in children with goiter. Environmental health perspectives. 2000;108(1):67.
27. Contempre B, Duale N, Dumont JE, Ngo B, Diplock A, Vanderpas J. Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population. Clinical endocrinology. 1992;36(6):579-83.
28. Wang M, Chen H. Forms and distribution of selenium at different depths and among particle size fractions of three Taiwan soils. Chemosphere. 2003;52(3):585-93.
29. Beckett GJ, MacDougall D, Nicol F, Arthur J. Inhibition of type I and type II iodothyronine deiodinase activity in rat liver, kidney and brain produced by selenium deficiency. Biochemical Journal. 1989;259(3):887-92.
30. Liu Y, Huang H, Zeng J, Sun C. Thyroid volume, goiter prevalence, and selenium levels in an iodine-sufficient area: a cross-sectional study. BMC Public Health. 2013;13(1):1.
31. Giray B, Hincal F, Teziç T, Ökten A, Gedik Y. Status of selenium and antioxidant enzymes of goitrous children is lower than healthy controls and nongoitrous children with high iodine deficiency. Biological trace element research. 2001;82(1):35-52.
32. Giray B, Hincal F. Oxidative DNA base damage, antioxidant enzyme activities and selenium status in highly iodine-deficient goitrous children. Free radical research. 2002;36(1):55-62.
33. Taylor EW. Selenium and cellular immunity. Biological trace element research. 1995;49(2):85-95.
34. Spallholz JE, Boylan L, Larsen HS. Advances in understanding selenium's role in the immune system. Annals of the New York Academy of Sciences. 1990;587(1):123-39.
35. Organization WH. Trace elements in human nutrition and health: World Health Organization; 1996.