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Serum Selenium Levels in Euthyroid Nodular Thyroid Diseases

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Abstract The thyroid gland is susceptible to nodulation. The mechanism responsible for the growth of only some follicular cells, which results in nodule formation, is not yet clear. Selenium deficiency may be a risk factor in the development of thyroid nodules. The aim of this study was to investigate the relationship between selenium levels in patients with euthyroid nodular thyroid disease. Seventy patients with a solitary euthyroid thyroid nodule, 70 patients with more than one euthyroid nodule, and 60 healthy patients without thyroid nodules were included in the study. Venous serum samples were stored at -80°C and analyzed the same day using spectrometry. The selenium levels of patients with multiple thyroid nodules, solitary nodules, and patients without nodules were 57.3 ± 14.8 μg/L; 58.8 ± 15.1 μg/L; and 57.6 ± 13.3 μg/L, respectively. The mean serum selenium level of all patients included in the study was 57.9 ± 14.4 μg/L. Although serum selenium levels were slightly higher in men, a statistically significant difference was not observed. In our study, a significant relationship between serum selenium levels and nodular thyroid disease was not seen. Our study was undertaken in an iodine sufficient region. Mean serum selenium levels were lower compared with many other studies, which may be associated with the low selenium content of the soil. Nodular thyroid disease shows multifactorial features. When our study is considered together with previous studies, serum selenium levels may considered to be effective on structural thyroid diseases if combined with additional factors such as severe iodine deficiency. Further studies are required to assess the role of selenium in thyroid nodule formation.

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Introduction

Thyroid nodules are masses that mostly arise with hyperplasia and/or hypertrophy of thyrocytes and can be distinguished from thyroid parenchyma using ultrasonography and palpation. The rate of diagnosed thyroid nodules in the general population ranges from 20 to 76 % using ultrasonography [1, 2]. The main clinical significance of thyroid nodules is related with the probability of developing thyroid cancer. It is thought that factors like heredity, genetic abnormalities, peripheral goitrogens, and lack of iodine has a risk on oncogenesis and nodulogenesis of the thyroids. However, the etiology of thyroid nodules has not yet been clearly explained. It is also not known why some patients develop solitary nodules and others develop multiple nodules.

Despite national iodine replacement programs, structural and functional thyroid disorders continue to be a major health concern in many countries. Therefore, the relationship of trace elements other than iodine with thyroid disorders was investigated. In many studies, there has been a significant relationship between serum selenium levels, which is one of the trace elements, and thyroid disorders [3–6]. Furthermore, the relationship between cancers of various organs with selenium deficiency has long been known [7, 8]. In the same way, selenium deficiency could be a risk factor for the development of thyroid nodules, but differing results on this issue have been reported [9–12].

Selenium is a structural component of more than 25 selenoproteins such as glutathione peroxidase, iodothyronine deiodinase, and thioredoxin reductase, and it has an important role in thyroid physiology [13–15]. Relative to organ weight, selenium is found in higher concentrations in the thyroid gland than in other organs and it has been known for many years that this concentration correlates with blood levels [16–18]. These factors lead to selenium being considered as the second basic building block of thyroid metabolism, after iodine [15].

In summary, the effects of selenium on tumorigenesis and thyroid metabolism pathophysiology have been shown in several trials. Therefore, we aimed to investigate whether serum selenium levels contributed to the formation of nodules in an iodine-sufficient region [19]. In addition, we evaluated patients with solitary nodules and multiple nodules separately. In doing so, we aimed to contribute to the discussion as to whether selenium affected the pathogenesis of solitary or multiple nodule formation.

Materials and Methods

Participants were recruited from one university's endocrine and internal medicine clinics. The study protocol was approved by the local ethics committee.

Included in the study were 70 patients with single euthyroid thyroid nodules (61 women (87.1 %) and 9 men (12.9 %)), 70 patients with multiple euthyroid thyroid nodules (66 women (94.3 %) and 4 men (5.7 %)), and a control group that comprised 60 people without euthyroid nodule formation (47 women (78.3 %) and 13 men (21.7 %)). For all 200 participants (174 women (87 %) and 36 men (13 %)), the demographic characteristics, physical examination, thyroid ultrasound, and biochemical tests were recorded. Informed consent was given by all participants. Blood samples used to study serum selenium levels were obtained during routine examinations and analyses. Sera obtained from participants were stored at −80 °C until all samples were collected. Patients who were using drugs that could affect the metabolism of thyroid hormones (e.g., antithyroid drug, L-thyroxine) and those with thyroid dysfunction or with any other comorbidities were excluded from the study. Also, none of the patients received selenium supplements.

Thyroid ultrasonography was performed using an ultrasound device with high frequency 12 MHz linear array transducer. Thyroid volumes were calculated according to the spherical ellipsoid formula: (volume = $\pi/6 \times$ anteroposterior diameter (cm) × width (cm) × length (cm)) [20]. Thyroid volumes greater than 25 mL in men and 18 mL in women were recorded as goiter [21]. Thyroid nodularity, nodule size, and nodule characteristics were recorded as recommended at 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [22]. Also, nodule volume was calculated using the same formula as used for thyroid volume. In the multinodular group, the dominant nodule was chosen for nodule volume calculation and suspicion estimation. With regard to nodule quantity, the multinodular group was stratified in four categories: two, three, four, and more than four nodules.

The serum selenium levels of all samples were analyzed using atomic absorption spectrometry. Selenium analysis was performed using an Ultra lamp current 20 mA, wavelength 196 nm, 1 nm band width, with a platform graphite tube EL08013009 Varian AA240 Zeeman background correction Z-type device. Palladium nitrate was used as a regulatory matrix and the equivalent for the calibration matrix 10, 20, 40, and 50 mg/L dose were used.

Parameters were analyzed using SPSS version 16.0 statistical software. Analyses of variations in selenium levels between groups were performed using ANOVA variance analysis and regression analysis. T-test was used to analyze continuous variables. A p value less than 0.05 was considered as statistical significance.

Results

Serum selenium levels are presented as mean + standard deviation. The mean selenium levels of participants with multiple nodules, single nodules, and without nodules were 57.3 ± 14.8; 58.8 ± 15.1, and 57.6 ± 13.3 μg/L, respectively. The mean serum selenium level of all patients in the study was 57.9 ± 14.4 μg/L. ANOVA variance analysis showed that selenium levels did not vary between groups ($p = 0.83$) (Fig. 1).

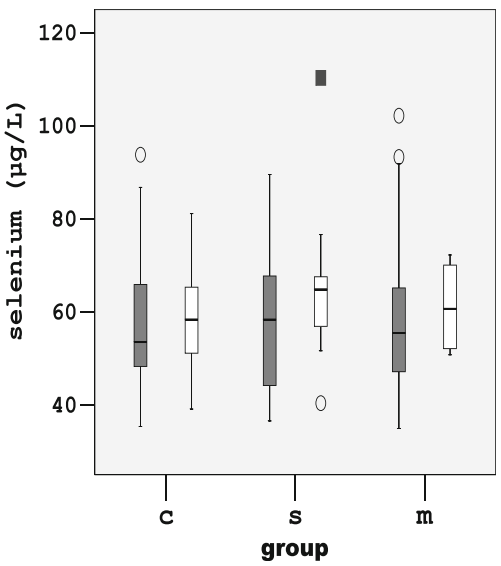

Fig. 1 Selenium levels, nodular thyroid disease, and sex relationship. *c* control group, *s* solitary group, *m* multinodular group. *Black boxplots* represent women participants. *White boxplots* represent men participants. *Circles* represent extreme values. The *square* represents the excess value

The serum selenium levels of women and men were 57.4 ± 14.4 and 61.4 ± 14.7 μg/L, respectively. Serum selenium levels were slightly higher in men; however, a statistically significant difference was not observed ($p = 0.18$). In addition, when male and female participants were assessed individually, we found that there was no correlation between serum selenium levels and nodule formation ($p < 0.05$). The mean age of our participants was 42.2 ± 13.9 years. The mean age of solitary group, multinodular group, and control group was 43.9 ± 13.2, 47.6 ± 12.4, and 33.8 ± 12.2, respectively. There was an age shift between groups. The multinodular group was the oldest group, and the control group was the youngest group. Linear regression analysis showed that age was not significantly predictive for serum selenium levels ($p = 0.59$) (Fig. 2).

In regard of sonographic features, there were 8 (5.7 %) hypoechoic nodules with high-risk features (microcalcification, irregular margins, rim calcifications with small extrusive soft tissue component, extrathyroidal extension, or round shape); 27 (19.3 %) hypoechoic nodules without high risk features; 95 (67.9 %) hyperechoic or isoechoic solid nodule, or partially cystic nodule with uniform eccentric solid area without high risk features; 10 (7.1 %) spongiform or partially cystic nodule without any of the high risk sonographic features [22]. Any of nodules were purely cystic. In the solitary group, the nodule volume was 0.7 mL (range, 0.1–21.7 mL). In the multinodulary group, the dominant nodule's volume was 1.0 mL (range, 0.2–42.7 mL). In our study, there were 24 (12 %) participants with two nodules, 11 (5.5 %) with three nodules, 9 (4.5 %) with four nodules, and 26 (13 %) participants had more than four nodules. There was no correlation between serum selenium levels and nodule volume ($p = 0.67$) and nodule quantity ($p = 0.90$).

As reported in preclinical and experimental studies, minimal 70 μg/L serum selenium levels are necessary for the maximal selenoprotein production; participants were evaluated in this respect. In our study, 166 participants had ≥70 μg/L serum selenium, and 34 participants had <70 μg/L. A statistically significant difference was not observed when a participant's serum selenium levels were evaluated for the presence of nodules relative to serum selenium levels under 70 μg/L ($p = 0.37$).

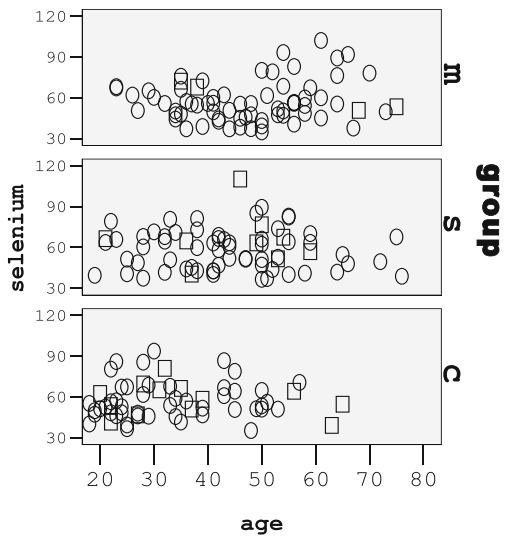

Fig. 2 Age distribution and serum selenium levels. *c* control group, *s* solitary group, *m* multinodular group. *Squares* represent men participants, and *circles* represent women participants

Serum selenium levels of participants who had goiter ($n = 82$; 41 %) and participants within normal thyroid volume ($n = 118$; 59 %) were 58.9 ± 15.2 and 56.62 ± 13.3 μg/L, respectively. A significant relationship in terms of goiter was not found ($p = 0.25$). When patients who had multiple nodules ($n = 70$) were assessed individually, there were 52 (74.28 %) patients with goiter and 18 without goiter (25.72 %). Their selenium levels were 57.0 ± 13.9 and 58.2 ± 17.7 μg/L, respectively. In the multinodular group, there was no significant relation between serum selenium levels and goiter ($p = 0.80$). When the solitary thyroid nodule group was assessed, there were 30 (42.85 %) patients with goiter and 40 (57.15 %) without goiter. Their selenium levels were 55.6 ± 12.8 and 61.1 ± 16.5 μg/L, respectively. There was no significant relation between serum selenium levels and goiter in the solitary nodule group ($p = 0.12$).

The mean TSH levels of participants with multiple nodules, single nodules, and without nodules were identified as 1.25 ± 0.72, 1.84 ± 1.10, and 2.35 ± 1.20 μU/mL, respectively. The mean TSH level of all patients in the study was 1.79 ± 1.19 μU/mL. There was no correlation between serum selenium levels and serum TSH levels ($p = 0.36$).

Discussion

In our study, with regard to nodular thyroid disease and serum selenium levels, a statistically significant correlation was not detected. The situation did not change after male and female participants in the same condition were divided into two groups. The Konya region has been determined to be of normal iodine status as a result of iodine prophylaxis that has been carried out since 2000 [19, 23]. Therefore, we did not assess the situation of iodine deficiency in patients. In our study, there was no correlation between selenium levels and sex or age. The low rate of male participants can lead to errors in the evaluation of the relationship between selenium levels and other parameters in men. In a study performed in Egypt, 22 patients with multiple thyroid nodules were compared with 15 control patients; their serum selenium levels were detected as 9.6 ± 1.24 and 11.7 ± 1.64 μg/L, respectively. The authors reported a significant relationship between low-level serum selenium and multinodular goiter ($p < 0.005$) [9]. The present study comprised adult groups and no correlation was detected between serum selenium levels and age. Serum selenium levels in this study were much lower than our study. This

situation can be explained by the dependence of racial and geographic variables. Samir et al.'s study was performed in an iodine deficiency area, and the effect of iodine deficiency was not evaluated. In addition, their study contained a limited number of participants; these conditions are the restricting features of their study [9]. In the study of Ozata et al., which was performed in Turkey, there was no significant correlation between the presence of goiter and serum selenium levels; nodular thyroid disease was not exclusively evaluated [24]. Serum selenium levels were lower in our study; however, similar results were found when considered in terms of the presence of goiter. This situation can be explained by the multifactorial features of structural thyroid diseases, i.e., nodules/follicles and goiter. Also, we aware that there should be some time preceding the appearance of the follicles/nodules and goiter. Thus, although there was no association between the presence of nodules and serum selenium, this is not proof that there was no selenium deficiency at the time of nodule formation.

In Denmark, in a mild iodine deficiency area, a study investigated the relationship between goiter and thyroid nodules with serum selenium levels, before and after iodine supplementation. Although a trend for risk of multiple thyroid nodule formation was identified with low serum selenium levels, it was not statistically significant ($p = 0.087$). No interaction was found between serum selenium levels and the development of single thyroid nodules ($p = 0.855$). Furthermore, the negative correlation between serum selenium levels (median 96.8 μg/L) and thyroid volume was statistically significant ($p = 0.006$). When the participants were divided into two groups as male and female, serum selenium levels showed an inverse correlation with the presence of goiter in women but no significant correlation was determined in men. When the participants were examined as before and after iodine supplementation, although the negative correlation continued its statistical significance in the before iodine supplementation group, this relationship lost its statistical significance in the after iodine supplementation group ($p = 0.021$ and 0.249, respectively) [10]. In a study conducted in Switzerland, in children with iodine and selenium deficiency, thyroid volume decline reduced after iodine supplementation in patients with selenium deficiency [25]. This confirms the theory of follicular cell hypertrophy and hyperplasia and cannot be explained by only one cause. When considered together with Rasmussen's study [10], this suggests that selenium and iodine deficiency may not be independent factors of thyroid disorders.

When we chronologically reviewed studies performed in Turkey, a significant correlation had been identified between serum selenium levels and thyroid nodules or goiter in the early 2000s. However, recent studies, some of which were performed by the same researchers, did not observe this correlation [11, 26, 27]. This situation may be associated with the reduction of iodine deficiency in Turkey through iodine supplementation. The main reason of uncorrelated serum selenium levels with nodular thyroid disorders and goiter in our study may be the alleviation of iodine deficiency, which is the most important contributor of thyroid disorders. Likewise, in a study conducted in a mild iodine deficiency area of France, the noncorrelation between selenium levels and thyroid nodulation could have been associated with mild levels of iodine deficiency. However, the correlation between serum selenium levels and goiter in the French study could be explained by the presence of contributors of thyroid disorders other than iodine [28, 29].

Normal serum selenium levels in terms of thyroid diseases have not yet been determined. However, experimental and preclinical studies have shown that levels higher than 70 μg/L are necessary for the production of sufficient selenoproteins [30–32]. Other studies have indicated that a ≥100 μg/L level of serum selenium is necessary in the prevention of goiter and autoimmune thyroid disease or anticancer activity [4, 33, 34]. When our study's data were considered according to serum selenium levels above or below 70 μg/L, there was no significant difference in terms of thyroid nodulation and goiter. The absence of other clinical studies in the literature on this subject and specific selenium levels (above 70 μg/L) raises the need for further investigation.

The effect level of serum selenium levels on the thyroid gland and its functions are still controversial. This is due to the heterogeneity of studies in terms of age, sex, severity of iodine deficiency, differences in study method, and differences in analysis of data; the subject may not yet have been sufficiently studied. Furthermore, an organism's selenium level is not yet a clear descriptor in terms of thyroid disorders. For now, it is known that serum selenium levels, GPX activity, urinary selenium, nail and hair selenium are associated with each other. However, each mutual relation has not yet been definitively determined [35–37].

The main source of selenium is soil content. The selenium levels of all nutrients of vegetables or animals are most influenced by soil content. The soil levels of selenium vary greatly in various regions of the world, from toxic levels to very low levels [37]. We think that our study's low serum selenium levels were due to the low levels of soil selenium content.

In conclusion, a statistically significant correlation between serum selenium levels and nodular thyroid disease was not identified in our study. The volunteers in our study came from the Middle Anatolia region of Turkey, and their serum selenium levels were determined lower than those found in other studies [38, 39]. This condition is associated with low soil selenium content. When our study is considered together with previous studies, serum selenium levels may be considered to be effective on thyroid structural diseases if combined with additional factors such as severe iodine deficiency. Therefore, assessment of selenium deficiency in terms of its public health impact and nodular thyroid disorders should be undertaken in further investigations.

Compliance with Ethical Standards The study protocol was approved by the local ethics committee.

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Ezzat S, Sarti DA, Cain DR, Braunstein GD (1994) Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 154(16):1838–1840
2. Tan GH, Gharib H (1997) Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 126(3):226–231
3. Kandhro GA, Kazi TG, Sirajuddin KNF, Kazi N, Afridi HI, Baig JA, Shah AQ, Wadhwa SK, Khan S, Arain MB (2011) Effects of selenium supplementation on iodine and thyroid hormone status in a selected population with goitre in Pakistan. Clin Lab 57(7–8): 575–585
4. Kishosha PA, Galukande M, Gakwaya AM (2011) Selenium deficiency a factor in endemic goiter persistence in sub-Saharan Africa. World J Surg 35(7):1540–1545. doi:10.1007/s00268-011-1096-5
5. Kvicala J, Zamrazil V (2003) Effect of iodine and selenium upon thyroid function. Cent Eur J Public Health 11(2):107–113
6. Triggiani V, Tafaro E, Giagulli VA, Sabba C, Resta F, Licchelli B, Guastamacchia E (2009) Role of iodine, selenium and other micronutrients in thyroid function and disorders. Endocr Metab Immune Disord Drug Targets 9(3):277–294
7. Salonen JT, Alfthan G, Huttunen JK, Puska P (1984) Association between serum selenium and the risk of cancer. Am J Epidemiol 120(3):342–349
8. Novotny L, Rauko P, Kombian SB, Edafiogho IO (2010) Selenium as a chemoprotective anti-cancer agent: reality or wishful thinking? Neoplasma 57(5):383–391
9. Samir M, el-Awady MY (1998) Serum selenium levels in multinodular goitre. Clin Otolaryngol Allied Sci 23(6):512–514
10. Rasmussen LB, Schomburg L, Kohrle J, Pedersen IB, Hollenbach B, Hog A, Ovesen L, Perrild H, Laurberg P (2011) Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. Eur J Endocrinol 164(4):585–590. doi:10.1530/EJE-10-1026
11. Giray B, Arnaud J, Sayek I, Favier A, Hincal F (2010) Trace elements status in multinodular goiter. J Trace Elem Med Biol 24(2): 106–110. doi:10.1016/j.jtemb.2009.11.003
12. Doupis J, Stavrianos C, Saltiki K, Mantzou E, Mastrokostopoulos A, Philippou G, Alevizaki M (2009) Thyroid volume, selenium levels and nutritional habits in a rural region in Albania. Hormones (Athens) 8(4):296–302
13. Weeks BS, Hanna MS, Cooperstein D (2012) Dietary selenium and selenoprotein function. Med Sci Monit 18(8):RA127–RA132
14. Drutel A, Archambeaud F, Caron P (2013) Selenium and the thyroid gland: more good news for clinicians. Clin Endocrinol 78(2): 155–164. doi:10.1111/cen.12066
15. Kohrle J, Gartner R (2009) Selenium and thyroid. Best Pract Res Clin Endocrinol Metab 23(6):815–827. doi:10.1016/j.beem.2009.08.002
16. Dickson RC, Tomlinson RH (1967) Selenium in blood and human tissues. Clin Chim Acta 16(2):311–321
17. Tiran B, Karpf E, Tiran A (1995) Age dependency of selenium and cadmium content in human liver, kidney, and thyroid. Arch Environ Health 50(3):242–246. doi:10.1080/00039896.1995.9940394
18. Aaseth J, Frey H, Glattre E, Norheim G, Ringstad J, Thomassen Y (1990) Selenium concentrations in the human thyroid gland. Biol Trace Elem Res 24(2):147–152
19. Kaya A (2007) The prevalence of goiter among children and adolescents in Konya and its surroundings. Scientific Research Project Thesis, Selcuk University, Konya
20. Knudsen N, Bols B, Bulow I, Jorgensen T, Perrild H, Ovesen L, Laurberg P (1999) Validation of ultrasonography of the thyroid gland for epidemiological purposes. Thyroid 9(11):1069–1074
21. Gutekunst R, Becker W, Hehrmann R, Olbricht T, Pfannenstiel P (1988) Ultrasonic diagnosis of the thyroid gland. Dtsch Med Wochenschr 113(27):1109–1112. doi:10.1055/s-2008-1067777
22. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L (2016) 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and Differentiated thyroid cancer. Thyroid 26(1):1–133. doi:10.1089/thy.2015.0020
23. Erdogan MF, Agbaht K, Altunsu T, Ozbas S, Yucesan F, Tezel B, Sargin C, Ilbeg I, Artik N, Kose R, Erdogan G (2009) Current iodine status in Turkey. J Endocrinol Investig 32(7):617–622. doi:10.1007/BF03346519
24. Ozata M, Salk M, Aydin A, Sayin S, Oktenli C, Beyhan Z, Isimer A, Ozdemir IC (1999) Iodine and zinc, but not selenium and copper, deficiency exists in a male Turkish population with endemic goiter. Biol Trace Elem Res 69(3):211–216
25. Zimmermann MB, Adou P, Torresani T, Zeder C, Hurrell RF (2000) Effect of oral iodized oil on thyroid size and thyroid hormone metabolism in children with concurrent selenium and iodine deficiency. Eur J Clin Nutr 54(3):209–213
26. Aydin K, Kendirci M, Kurtoglu S, Karakucuk EI, Kiris A (2002) Iodine and selenium deficiency in school-children in an endemic goiter area in Turkey. J Pediatr Endocrinol Metab 15(7):1027–1031
27. Giray B, Hincal F, Tezic T, Okten A, Gedik Y (2001) Status of selenium and antioxidant enzymes of goitrous children is lower than healthy controls and nongoitrous children with high iodine deficiency. Biol Trace Elem Res 82(1–3):35–52. doi:10.1385/BTER:82:1-3:035
28. Derumeaux H, Valeix P, Castetbon K, Bensimon M, Boutron-Ruault MC, Arnaud J, Hercberg S (2003) Association of selenium with thyroid volume and echostructure in 35- to 60-year-old French adults. Eur J Endocrinol 148(3):309–315
29. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briancon S (2004) The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 164(21):2335–2342. doi:10.1001/archinte.164.21.2335
30. Zhang Z, Tian Y, Yang X, Xia Y (1998) Effect of dietary selenium on the activities of glutathione peroxidase and deiodinase in rat liver. Wei Sheng Yan Jiu 27(3):209–211
31. Neve J (1991) Methods in determination of selenium states. J Trace Elem Electrolytes Health Dis 5(1):1–17
32. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, Marshall JR, Clark LC (2002) Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the nutritional prevention of cancer trial. Cancer Epidemiol Biomark Prev 11(7):630–639
33. Rayman MP (2005) Selenium in cancer prevention: a review of the evidence and mechanism of action. Proc Nutr Soc 64(4):527–542

34. Wertenbruch T, Willenberg HS, Sagert C, Nguyen TB, Bahlo M, Feldkamp J, Groeger C, Hermsen D, Scherbaum WA, Schott M (2007) Serum selenium levels in patients with remission and relapse of graves' disease. Med Chem 3(3):281–284
35. Robinson MF, Thomson CD, Jenkinson CP, Luzhen G, Whanger PD (1997) Long-term supplementation with selenate and selenomethionine: urinary excretion by New Zealand women. Br J Nutr 77(4):551–563
36. Kohrle J, Jakob F, Contempre B, Dumont JE (2005) Selenium, the thyroid, and the endocrine system. Endocr Rev 26(7):944–984. doi: 10.1210/er.2001-0034
37. Mehdi Y, Hornick JL, Istasse L, Dufrasne I (2013) Selenium in the environment, metabolism and involvement in body functions. Molecules 18(3):3292–3311. doi:10.3390/molecules18033292
38. Giray B, Hıncal F (2004) Selenium status in Turkey: possible link between status of selenium, iodine, antioxi- dant enzymes and oxidative DNA damage. J Radioanal Nucl Chem 259:447–451
39. Harmankaya M (2009) Determination of soil and wheat selenium levels in Central Anatolia and investigation of response of different wheat genotypes to selenium fertilization. master's thesis, Selçuk University, Konya