HORMONES 2010, 9(3):263-268

Research paper

Relationship between serum zinc levels, thyroid hormones and thyroid volume following successful iodine supplementation

Sibel Ertek[1], Arrigo FG Cicero[2], Omur Caglar[3], Gurbuz Erdogan[1]

[1]Ufuk University Medical Faculty, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey, [2]Bologna University, Atherosclerosis and Metabolic Diseases Research Center, Internal Medicine, Aging & Kidney Diseases Department, Bologna, Italy, [3]Ufuk University Medical Faculty, Department of Radiology, Ankara, Turkey

ABSTRACT

OBJECTIVE: Zinc is essential for many biochemical processes and also for cell proliferation. Thyroid hormones influence zinc metabolism by affecting zinc absorption and excretion. Additionally, zinc deficiency affects thyroid function. The aim of the present study was to evaluate a possible association of zinc levels with thyroid volume, thyroid hormones and thyroid autoantibody levels in healthy subjects, patients with autoimmune thyroid disease (AITD) and patients with nodular goitre following successful iodine supplementation. This is a cross-sectional study in which 201 subjects who were not under medical treatment and did not have previous thyroid surgery or radio-iodine treatment were evaluated. Seventy patients had nodular goitre, 67 AITD and 64 had normal thyroid. Thyroid volume was calculated by ultrasonographic measurements. Serum free T4, T3, TSH, anti-thyroglobulin and anti-thyroid peroxidase levels were determined by appropriate methodology.RESULTS: In patients with normal thyroid, zinc levels were significantly positively correlated with free T3 levels ($p<0.001$). In the nodular goitre group, thyroid volume was negatively correlated with TSH and circulating zinc levels ($p=0.014$ and $p=0.045$, respectively). In the AITD group, thyroid autoantibodies and zinc were significantly positively correlated. Multiple regression analysis revealed a significant relationship between thyroid volume and zinc only in the patients with nodular goitre ($p=0.043$). CONCLUSION: There was significant correlation of serum zinc levels with thyroid volume in nodular goitre patients, with thyroid autoantibodies in AITD and with free T3 in patients with normal thyroid.

Key words: Autoimmune thyroiditis, Chronic thyroiditis, Goitre, Iodine deficiency, Thyroid, Thyroid hormone metabolism, Zinc

Address for correspondence:
Sibel Ertek, MD, Department of Endocrinology and Metabolic Diseases, Ufuk University, Dr. Ridvan Ege Hospital, Mevlana Bulvari 86-88, 06520 Balgat- Ankara, Turkey, Tel: +90 312 204 40 00/ 4230, Fax: +90 312 204 40 55, E-mail: sibelertek@yahoo.it

Received 11-01-10, Revised 20-05-10, Accepted 10-06-10

INTRODUCTION

Zinc is an important element for numerous biochemical processes as well as for cell proliferation. Zinc is extensively studied by bioinorganic chemistry and it is known that there are many metalloproteins with specific enzymatic activity containing zinc. Carbonic anhydrase, liver alcohol dehydrogenase and alkaline phosphatase are some examples of zinc enzymes.[1]

Thyroid function influences zinc metabolism. In a study carried out in nephrectomized rats, it was observed that reduced thyroid function was strongly related to low serum zinc level.[2] Prasad et al reported that thyroid hormones modulate zinc transport activity in rat renal and intestinal brush-border membrane.[3] The evaluation of tissue specimens of 72 patients according to their content and coefficient of variation of iodine, zinc and selenium revealed a significant relationship between these elements and thyroid hormones and TSH blood levels.[4] In a German epidemiologic study in which 5932 clinically healthy, subjects were tested to evaluate iodine status and goitre prevalence, a significant negative relationship was detected between thyroid volume and zinc levels in subjects older than 40 years, although in other age groups there was no correlation between thyroid volume, iodine status and serum zinc levels.[5] Erytrocyte zinc and carbonic anhydrase enzyme levels are altered in patients with Graves' disease. Based on this observation it has been suggested that erythrocyte zinc levels could be used as an index of thyroid status in the preceding months in the same way that glycohemoglobin levels are employed in diabetics. This index can also be applied for the differentiation between Graves' disease and other forms of thyrotoxicosis.[6-8]

Zinc has some effects on TSH and thyroid hormone levels. Furthermore, zinc supplementation improves thymic and immune functions in children with Down's syndrome.[9,10] Specifically, children with Down's syndrome and low zinc levels have a higher incidence of subclinical hypothyroidism and higher TSH levels that can be improved by zinc replacement.[10]

In Turkey, legislation necessitating the iodization of table salt was started in 1999 by the addition of 50-70 mg/kg potassium iodide or 25-40 mg/kg potassium iodine in order to prevent endemic goitre caused by iodine deficiency. In a recent study evaluating goitre prevalence in school age children in Ankara, it was shown that the iodine sufficiency was reached within 7 years of initiation of countrywide prophylaxis.[11,12] In the present study, we aimed to evaluate a possible relationship of serum zinc levels with thyroid hormones, thyroid volume, anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies (Ab) in subjects with either normal thyroid, autoimmune thyroid disease (AITD) or nodular goitre in the Turkish population of Ankara following successful iodine supplementation.

METHODS

We evaluated 201 subjects (62 men, 139 women) who consecutively visited the Ufuk University Department of Endocrinology for thyroid disease screening, excluding those having received any medical or surgical treatment for the thyroid at any time of their life or subjects with a history of radio-iodine treatment. All patients were older than 18 years and all gave informed consent. The study was approved by the regional Ethics Committee.

Patients with normal thyroid function, negative thyroid autoantibodies and echographically normal thyroid were classified as normal, independent of their calculated thyroid volume. Patients with echographically normal thyroid but with thyroid nodules were classified as having nodular goiter and those with heterogenous parenchyma of the thyroid and positive thyroid antibodies were grouped as AITD. Thyroid nodules smaller than 2 mm in AITD patients were not considered as nodules. Patients with both thyroid nodules and heterogenous thyroid paranchyma were excluded.

RADIOLOGICAL PARAMETERS

Ultrasonographic evaluation was conducted by using a GE LOGIQ 10 ultrasonography device with a 7.5 MHz linear probe, by the one radiologist, who was not aware of the laboratory data of the patients. The thyroid volume was calculated by ultrasonographic measurements using the formula "length x width x depth x pi/6" for each lobe and the sum was accepted as total thyroid volume.[13] Their urine iodine levels were measured to exclude iodine deficiency.

Biochemical parameters

Serum free T4 and T3, TSH, anti-thyroglobulin and anti-thyroid peroxidase levels were measured by the standardized electrochemiluminescence immunoassay (ECLIA) method and serum zinc was measured spectrophotometrically.

The urinary iodine concentration of 30 patients, randomly selected, was determined in a spot morning urine sample by the calorimetric ceric ion arsenous acid wet-ash method based on Sandell Kolthoff reaction using Fisher reagents and Genesis Spectronic 20 spectrophotometer, in order to exclude iodine deficiency (Fisher Scientific, Laughborough, UK).

Statistical methods

A full descriptive analysis of the available data was carried out using a Kolmogorov-Smirnov normality test. One-way ANOVA was applied for evaluation of difference between the two sexes and for difference between thyroid diseases. The Tukey HSD test was carried out to compare thyroid function tests, thyroid volume, age, thyroid autoantibodies and zinc levels in three thyroid diseases. Bivariate correlations were performed for all patients, and also for both sexes and each thyroid group for the same variables. Pearson's bivariate correlation analysis was carried out when evaluating two normally distributed parameters; otherwise, we performed Spearman's correlation analysis. Regression analysis was carried out to test correlations between thyroid volume and TSH, free T4 and T3, anti-TG, anti-TPO antibodies and zinc levels. Parameters that were not normally distributed were normalised by log-transformation before regression analysis. P values lower than 0.05 were considered as significant. All tests were carried out with the help of SPSS 12.0, version for Windows.

RESULTS

In 30 patients, randomly selected urinary iodine excretion was normal with a mean value of 219.63±110.61 (SD) μg/L.

Seventy subjects (34.8%) had nodular goitre, 67 (33.3%) AITD and 64 (31.8%) had normal thyroid, as previously defined.

Women were significantly younger ($p<0.001$) and had lower thyroid volume ($p=0.009$) than men, but they had significantly higher ($p=0.046$) anti-TPO antibody levels (Table 1).

Echographical pattern: 27% of women had normal thyroid, 33% multinodular goitre and 40% AITD, while 43% of men had normal thyroid, 39% multinodular goitre and 18% AITD (Pearson Chi-Square 10.78, 2DF, P= 0.005).

Repeating the analyses by thyroid disease, TSH ($p=0.003$) and both thyroid Ab levels were significantly different among the three groups ($p<0.001$) and higher in the AITD group (via the Tukey HSD test $p=0.011$ for TSH, $p<0.001$ for both thyroid autoantibodies).

Table 1. Values of various parameters in males and females (mean ±SD)

	Males	Females	p value*
N	62	139	---
Age (years)	51.3 ± 10.9	42.2 ± 14.8	0.001
Thyroid volume (ml)	23.7 ± 14.2	16.04 ± 15.5	0.009
TSH (mIU/mL)	1.89 ± 1.27	3.39 ± 3.44	0.070
Free T4 (pmol/L)	1.33 ± 0.28	1.23 ± 0.25	0,057
Free T3 (pmol/L)	0.39 ± 0.40	0.35 ± 0.40	0,600
Anti-thyroglobulin antibody (IU/mL)	94.27 ± 91.15	195.84 ± 143.06	0,068
Anti-TPO antibody (IU/mL)	54.08 ± 47.72	107.87 ± 104.63	0.046
Zinc (μg/dL)	72.15 ± 17.65	73.29 ± 11.75	0,601

*t-test for normally distributed variables or the Mann-Whitney test (for non-normally distributed variables). Statistically significant differences if p<0.05.

Taking into consideration the whole patient sample, a significant positive correlation was observed between thyroid volume and age (p=0.006), also between TSH levels and free T4, anti-thyroglobulin and anti-TPO Ab levels (in all three p<0.001).

In men, a significant correlation between both thyroid antibodies and free T4 levels (p<0.001 for both) was observed, while thyroid volume (p=0.010) and age (p=0.015) were negatively correlated with TSH levels. There was no significant correlation between thyroid volume and zinc levels, though zinc levels were negatively correlated with free T3 levels (p=0.049) in men.

In women, thyroid volume was not related to any of the parameters studied, but thyroid auto-antibodies (p<0.001), free T4 (negatively) (p<0.001) and zinc levels (p=0.042) were significantly correlated with TSH levels.

In the group with normal thyroid, the thyroid volume was positively correlated with thyroid autoantibody levels (p=0.001 for anti-TG and p<0.001 for anti TPO). The TSH was negatively correlated only with free T4 levels in this group. Zinc (p<0.001) was significantly positively correlated with free T3 (p<0.001).

In the nodular goiter group, the thyroid volume was negatively correlated with TSH (p=0.014) and zinc levels (p=0.045). Zinc was also negatively correlated with free T3 (p=0.007) and thyroid auto-antibodies were negatively correlated with age (p=0.044 for anti-TG and p=0.001 for anti-TPO).

In patients with AITD, thyroid volume was not correlated with any of the parameters studied, but TSH levels were significantly correlated with thyroid autoantibodies (p=0.000 for anti-TG and p=0.008 for anti-TPO) and zinc levels (p=0.049). There was also a strong negative correlation between TSH levels and free T4 and T3 levels (p=0.001 and p=0.002, respectively). Serum zinc levels were also significantly correlated with anti-thyroglobulin Ab levels in this group (p=0.002).

Regression analysis revealed a significant relationship between thyroid volume and zinc only in nodular goitre patients (p=0.043) but neither in AITD patient (p=0.081) nor in the normal group (p=0.429) was this the case. In the normal group, thyroid volume was significantly correlated only with TSH levels (p=0.027). (Figure 1).

DISCUSSION

It is well known that iodine deficiency affects thyroid volume and function.[14] The effects of selenium, magnesium, copper, iron, cobalt and manganese on the thyroid have been studied in animals and humans.[15-19] Zinc is an essential trace metal for catalytic activities of many enzymes involved in the metabolism of hormones. Zinc effects on thyroid hormones are complex and include both synthesis and mode of action.[20] Thyroid transcription factors which are essential for modulation of gene expression contain zinc at cysteine residues.[21] Nevertheless, the effects of zinc on thyroid hormone levels and the thyroid gland in general are still not clear. Animal and human studies have yielded conflicting results, low T3 levels being found in some patients with zinc deficiency.[20] Interestingly, Maxwell and Volpe observed that, while the thyroid hormone levels and metabolic rates of two zinc-deficient sub-

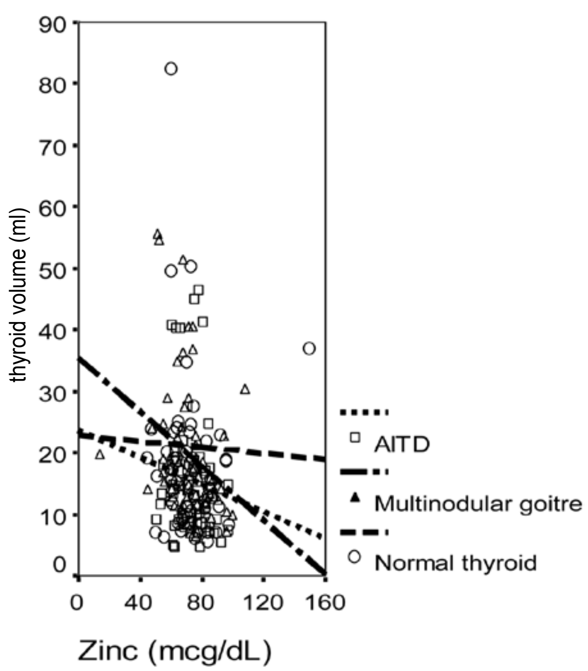

Figure 1. Relationship between thyroid volume (ml) and zinc levels (μg/dl) in each group of thyroid disease. P values for the relationship between zinc levels and thyroid volume in each group were: for normal thyroid group p= 0.924; for nodular goitre p= 0.029, for AITD group p= 0.336.

jects were comparable, zinc supplementation (26.4 mg/day as zinc gluconate) increased both free and total T3 and T4 levels in one subject, but increased only total T3 in the other subject at 4 months, while resting metabolic rate was increased in both.[22] The studies concerning the effects of zinc supplementation on thyroid function have generally been carried out in small groups. In one such study in which 25 mg of zinc was given to euthyroid and hyperthyroid patients, it was shown that zinc depresses TSH levels in healthy subjects.[23] In our study, we investigated a relatively large sample and found a linear relationship between TSH and zinc levels in women in all three groups of thyroid diseases evaluated.

Our study demonstrated that the relationship of zinc to various thyroid parameters differs in the three studied groups. Specifically, in the nodular thyroid group zinc levels were negatively correlated with thyroid volume and free T_3, whereas in the normal thyroid group, zinc was positively correlated with free T_3. Previous iodine deficiency might be an important factor explaining the findings in the nodular thyroid group even in the absence of current iodine deficiency.

Data as to whether zinc deficiency may increase nodule formation or cause goitrogenous growth of the thyroid is lacking. This could be studied by large-scale prospective studies, especially in areas of previous iodine deficiency such as Ankara.

In patients with AITD, TSH was correlated with zinc and thyroid autoantibodies. This result cannot be explained by an antioxidant effect of this element since this is not in accordance with the known effects of antioxidants on the thyroid.[24] Zinc deficiency is common in children with Down's syndrome, who also have higher incidence of hypothyroidism improves which zinc supplementation.[9] The effects of zinc have been studied in detail in patients with Down's syndrome while also examining a possible relationship with other comorbidities of this syndrome.[9,25] Although no relationship between zinc and thyroid autoantibodies was detected in children with Down's syndrome, the incidence of antibodies was reported to be up to 25%.[26] Other studies have shown the importance of evaluating patients with only chronic thyroiditis with regard to the effects of zinc. The results of the above studies offer little to our understanding of the role of zinc on thyroid function in subjects without Down's syndrome. Nevertheless, studies of zinc in Down's syndrome, are in concordance with the results of our study.

Our regression analysis revealed a significant relationship between serum zinc levels and thyroid volume only in patients with nodular goiter. Possible effects of previous iodine deficiency on the development of the thyroid nodules and the goitrogenous state of the gland might play a role in this association, a hypothesis based on the fact that the volume of the thyroid gland in the other groups was not related with zinc levels. Even with normal iodine levels, zinc may have goitrogenous effect in this group of patients. This relationship between goitre and zinc level is in concordance with an old study by Napolitano et al in children with Down's syndrome, which are in conflict with the study of Hampel et al.[5,9] Our study is the first which analyzes zinc levels separately in subjects with either normal thyroid or nodular goiter as well as in patients with AITD. This distinction could well be important in the evaluation of the effects of zinc both on thyroid diseases or in subjects with normal thyroid. Moreover, zinc levels measurements in thyroid tissue together with oxidant/antioxidant balance evaluation could also be of assistance in explaining the mechanism.[27] Finally, thyroid nodules in patients with AITD should also be examined separately to assess the effect of zinc in this group.

The effects of zinc in states of deficiency of other trace elements is also not clear.[27] Although our patients were not currently iodine deficient, they had previously been exposed to an iodine deficient environment. Hence our finding may not apply to other populations. Relationship between thyroid volume, thyroid functions and zinc in different thyroid diseases with and without deficiencies of other elements should be assessed.

Conclusions. Significant relationships between thyroid volume and serum zinc levels in nodular goitre patients, between thyroid autoantibodies and zinc in AITD patients and between free T_3 and zinc in subjects with normal thyroid were detected. The findings underline the importance of studying the link of serum zinc levels with thyroid gland function in groups of well defined thyroid disorders in order to draw meaningful conclusions with regard to the role of zinc in thyroid physiology and nosology.

Declaration of interest: None of the authors have any conflict of interest.

Funding: No funding was contributed.

REFERENCES:

1. Bertini I 1982 The Coordination Chemistry of Metalloenzymes. The Role of Metals in Reactions Involving water, dioxygen, and related species. The Coordination Properties of the active site of zinc enzymes. In: Bertini I, Drago RS, Luchinat C, (eds), Kluwer Boston Inc. Canada. Published by Riedel Publishing Company. NATO Advanced Study Institute, San Miniato-Italy, pp; 1-3.
2. Chen SM, Kuo CD, Ho LT, Liao JF, 2002 Effect of hypothyroidism on intestinal zinc absorption and renal zinc disposal in five-sixth nephrectomized rats. Jpn J Physiol 55: 211-219.
3. Prasad R, Kumar V, Kumar R, Singh KP, 1999 Thyroid hormones modulate zinc transport activity of rat intestinal and renal brush-border membrane. Am J Physiol 276: E774-782.
4. Bellisola G, Bratter P, Cinque G, et al, 1998 The TSH-dependent variation of the essential elements iodine, selenium and zinc within human thyroid tissues. J Trace Elem Med Biol 12: 177-182.
5. Hampel R, Kuhlberg T, Schneider KP, Glass A, Zollner H, 1997 Serum zinc levels and goitre epidemiology in Germany. Z Ernahrungswiss 36: 12-15.
6. Varga F, Tarjan G, Steczek K, Foldes J, 1994 Zn content of erythrocytes in overt and subclinical hypothyroidism. Orv Hetil 135: 1183-1185.
7. Yoshida K, 2007 Erythrocyte carbonic anhydrase I and zinc concentrations in thyrotoxicosis reflect integrated thyroid hormone levels over the previous few months. Rinsho Byori 55: 560-565.
8. Yoshida K, Kiso Y, Watanabe TK, et al, 1990 Erythrocyte zinc in hyperthyroidism: reflection of integrated thyroid hormone levels over the previous few months. Metabolism 39: 182-186.
9. Napolitano G, Palka G, Lio S, et al, 1990 Is zinc deficiency a cause of subclinical hypothyroidism in Down syndrome? Ann Genet 33: 9-15.
10. Bucci I, Napolitano G, Giuliani C, et al, 1999 Zinc sulphate supplementation improves thyroid function in hypozincemic Down children. Biol Trace Elem Res 67: 257-268.
11. Erdogan G, Erdogan MF, Emral R, et al, 2002 Iodine status and goitre prevalence in Turkey before mandatory iodization. J Endocrinol Invest 25: 224-228.
12. Erdogan MF, Demir O, Emral R, Kamel AN, Erdogan G, 2009 More than a decade of iodine prophylaxis is needed to eradicate goitre among school age children in a moderately iodine-deficient region. Thyroid 19: 265-268.
13. Baskin HJ 2008 Anatomy and Anomalies. In: Baskin HJ, Duick DS, Levine RA (eds) Thyroid Ultrasound and Ultrasound-guided FNA 2nd ed. Springer Science + Business Media, LLC, USA; pp, 47-48.
14. Zimmerman MB, 2009 Iodine deficiency. Endoc Rev 30: 376-408.
15. Erdogan MF, Erdogan G, Sav H, Gullu S, Kamel N, 2001 Endemic goitre, thiocyanate overload and selenium status in school-age children. Biol Trace Elem Res 79: 121-130.
16. Hess SJ, Zimmerman MB, Arnold M, Langhans W, Hurrel RF, 2002 Iron deficiency anemia reduces thyroid peroxidase activity in rats. J Nutr 132: 1951-1955.
17. Soldin OP, Aschner M, 2007 Effect of manganese on thyroid hormone homeostasis:potential links. Neurotoxicology 28: 951-956.
18. Kubasova ED, Kubasov RV, 2008 Effect of trace elements on thyroid structural and functional state (a review). Gig Sanit 5: 79-81.
19. Triggiani V, Tafaro E, Giagulli VA, et al, 2009 Role of iodine, selenium and other micronutrients in thyroid function and disorders. Endocr Metab Immune Disord Drug Targets Sept (Epub ahead of print). PMID: 19594417.
20. Arthur JR, Beckett GJ, 1999 Thyroid function. British Medical Bulletin 55: 658-668.
21. Civitareale D, Saiardi A, Falasca P, 1994 Purification and characterization of thyroid transcription factor 2. Biochem J 304: 981-985.
22. Maxwell C, Volpe SL, 2007 Effect of zinc supplementation on thyroid hormone function. A case study of two college females. Ann Nutr Metab 51: 188-194.
23. Faroogi L, Mazeto GM, Shuhama T, Brandao-Neto J, 2000 Effects of single venous dose of zinc on thyroid status in healthy individuals and patients with Graves' disease. Met Based Drugs 7: 151-155.
24. Burek CL, Rose NL, 2008 Autoimmune thyroiditis and ROS. Autoimmunity Rev 7: 530-537.
25. Romano C, Pettinato R, Ragusa L, Barone C, Alberti A, Failla O, 2002 Is there a relationship between zinc and the peculiar comorbidities of Down syndrome? Downs Synd Res Pract 8: 25-28.
26. Kanavin O, Scott H, Fausa O, Ek J, Gaarder PI, Brandtzaeg P, 1988 Immunological studies in patients with Down's syndrome. Measurements of autoantibodies and serum antibodies to dietary antigens in relation to zinc levels. Acat Med Scand 224: 473-477.
27. Kucharzewski M, Braziewicz J, Majewska U, Gozdz S, 2003 Copper, zinc and selenium in whole blood and thyroid tissue of people with various thyroid diseases. Biol Trace Elem Res 93: 9-18.