SERUM LEVELS OF CALCIUM, SELENIUM, MAGNESIUM, PHOSPHORUS, CHROMIUM, COPPER AND IRON – THEIR RELATION TO ZINC IN RATS WITH INDUCED HYPOTHYROIDISM

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SUMMARY – There is an important relation between thyroid hormones and zinc. Establishment of low zinc levels in hypothyroidism and high levels in hyperthyroidism is a significant proof of this relation. The aim of the present study was to explore changes in serum levels of some elements and their relation to zinc in rats with hypothyroidism. Thirty adult male rats of Sprague-Dawley type were divided into 3 equal groups: group 1, control; group 2, sham-hypothyroidism group supplemented with 10 mg/kg serum physiologic i.p. for 4 weeks; and group 3, hypothyroidism group supplemented with 10 mg/kg propylthiouracil i.p. for 4 weeks. Blood samples were collected from all animals by decapitation and serum calcium, phosphorus, chromium, copper, iron, magnesium, selenium and zinc levels were analyzed using an atomic emission apparatus. Group 3 had lower calcium, selenium and zinc levels, and higher chromium, copper, iron and phosphorus levels ($p<0.01$ all) relative to groups 1 and 2. Study parameters did not differ between groups 1 and 2. Results obtained in this study indicate that hypothyroidism leads to changes in serum levels of some elements in rats. These changes may be associated with reduced zinc levels in hypothyroidism.

Key words: *Selenium; Copper; Zinc; Iron; Hypothyroidism; Rat*

Introduction

Zinc is a trace element, which is required for the activity of more than 300 enzymes[1]. It is also a structural component of several enzymes responsible for energy metabolism, including carbonic anhydrase, alkaline phosphatase, lactate dehydrogenase, carboxypeptidase, DNA-dependent RNA polymerase, and DNA polymerase[1,2]. Zinc, which plays an important role in the endocrine system due to its above-mentioned effects, is also necessary for optimal activity of many hormones, including thyroid hormones[3]. Low zinc concentrations have been reported in hypothyroidism and high zinc concentrations in hyperthyroidism, both of which are diseases of the thyroid gland[4]. Zinc acts on the hypothalamus and hypophysis, and is necessary for the synthesis of thyrotropin-releasing hormone (TRH)[5,6]. It is also required for the activity of the enzyme 1,5'-deiodinase, which converts biologically less active T_4 (thyroxine) to its active form T_3 (triiodothyronine)[7]. Both trace elements and thyroid hormones play important roles in the human body. Due to all these effects, zinc can be said to be a micro food associated with thyroid hormones[5]. Results of previous studies demonstrate that changes occur in serum levels of various elements, zinc in particular, in case of impaired thyroid functioning[8,9]. Kucharzewski *et al.*[10] report that levels of zinc and selenium were significantly low in thyroid tissues of patients with

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thyroid cancer. Iodine deficiency affects the thyroid function[11,12]. Similarly, in another study, zinc levels were lower in thyroid cancer patients than in normal subjects; while serum copper in the patients increased, the levels of iron, magnesium and manganese significantly decreased postoperatively[13]. The levels of zinc, manganese and copper were shown to change markedly in the erythrocyte and brain tissue of rats with induced iodine deficiency[14]. As reported by Dolev *et al.*[15], not only plasma zinc levels, but also peripheral blood mononuclear cell zinc decreased in hypothyroid subjects. Previous studies indicate that the levels of some elements may change in relation to changes in thyroid activity. The present study aimed to explore changes in serum levels of some elements and their relation to zinc in rats with induced hypothyroidism.

Materials and Methods

This study was carried out at Experimental Medicine Research and Application Center (SUDAM) of Selcuk University on the rats supplied thence. The study included 30 adult male rats of Sprague-Dawley type, weighing 190-230 g, which were allocated to groups as follows: group 1: control group without any intervention (n=10); group 2: sham- propylthiouracil (PTU) hypothyroidism group supplemented with 10 mg/kg serum physiologic i.p. for 4 weeks (n=10); and group 3: PTU hypothyroidism group supplemented with 10 mg/kg PTU for 4 weeks (n=10)[16].

Feeding of experimental animals

Experimental animals were given 10 g feed *per* 100 grams of body weight daily. They were kept in an environment with standard room temperature (21±1 °C) and 12 h dark/12 h light cycle. All injections were given between 09.00 and 10.00 a.m. At the end of the 4-week period, blood samples were collected from all animals by decapitation at 09.00-10.00 a.m. to be used in the analyses. The samples were stored at -80 °C until analysis.

Sham-hypothyroidism

The experimental animals were supplemented with 0.1 NaOH/0.9% NaCl (1 mL/250 g) as placebo by intraperitoneal (i.p.) route, which dissolved PTU for 4 weeks.

Propylthiouracil supplementation

In order to induce hypothyroidism, 6-n-propyl-2-thiouracil (PTU, Sigma Chemical Co., Dorset, UK) was dissolved in 0.1 NaOH/0.9% NaCl and administered as 10 mg/kg/day (1 mL/250 g) by i.p. injection for 4 weeks.

Biochemical analyses

At the end of the experimental part of the study, serum samples were taken from all animals by decapitation to determine calcium, phosphorus, chromium, iron, magnesium, selenium and zinc levels. Analyses of the study parameters were carried out using an inductively coupled plasma emission spectrophotometry (ICP-AES, Varian Australia Pty Ltd., Australia) atomic emission apparatus at the Soil Department, Faculty of Agriculture, Selcuk University. The results were expressed as mg/L.

Statistical analysis

Statistical analysis was done using the SPSS statistical software. Results were expressed as mean ± standard deviation. Kruskal-Wallis variance analysis was used for between-group comparison and Mann Whitney *U* test was applied for the level of significance at $p<0.005$.

Results and Discussion

Hypothyroidism group (group 3) had lower calcium, selenium and zinc levels ($p<0.01$) (Table 1), and higher chromium, copper, iron and phosphorus levels ($p<0.01$) (Table 2) as compared with sham-hypothyroidism and control groups. There were no differences between control and sham-hypothyroidism groups for the mentioned elements (Tables 1 and 2).

In our study, the lowest zinc levels were obtained in the hypothyroidism group (group 3). One of the endocrine functions associated with zinc are changes in thyroid hormone metabolism and energy consumption of humans and animals who are on a low-zinc diet[4]. Observing shrinkage in thyroid glands of guinea pigs with zinc defect, and parallel degenerative changes, as well as atrophy in thyroid follicles, Gupta *et al.*[17] report that zinc deficiency could directly influence thyroid hormone synthesis. Likewise, Hartoma *et al.*[18] argue that zinc could directly affect thy-

Table 1. Serum calcium, selenium, zinc and magnesium levels in study groups (mg/L)

Group (n=10 each)	Calcium	Selenium	Zinc	Magnesium
1 Control	195.00±11.55[a]	2.71±0.25[a]	3.75±0.40[a]	46.50±9.57
2 Sham-hypothyroidism	194.00±10.60[a]	2.76±0.16[a]	3.60±0.30[a]	45.75±8.75
3 Hypothyroidism	168.00±09.50[b]	1.55±0.15[b]	2.25±0.23[b]	44.67±9.25
p	0.01	0.01	0.01	

Difference between the means with different superscripts in the same column is statistically significant ($p<0.01$) (a>b).

Table 2. Serum phosphorus, chromium, copper and iron levels in study groups (mg/L)

Group (n=10 each)	Phosphorus	Chromium	Copper	Iron
1 Control	270.80±20.22[b]	0.08±0.05[b]	2.91±0.55[b]	3.65±0.65[b]
2 Sham-hypothyroidism	274.76±22.50[b]	0.08±0.05[b]	3.01±0.75[b]	3.72±0.60[b]
3 Hypothyroidism	337.45±25.75[a]	0.14±0.05[a]	4.59±0.77[a]	4.75±0.65[a]
p	0.01	0.01	0.01	0.01

Difference between the means with different superscripts in the same column is statistically significant ($p<0.01$) (a>b).

roid function and that it could play a role in thyroid hormone metabolism by increasing the production of thyroxin-binding proteins. Similar findings have been reported by Dhawan[19]. The effect of zinc on thyroid hormone levels was also shown by Wada and King[7]. However, it is clear that this relation is not unidirectional. Thus, a decrease in thyroid hormones leads to the suppression of zinc levels[4]. In a study including 34 hypothyroid patients, serum zinc content was shown to be remarkably decreased[20]. However, Alturfan *et al.*[21] report that methimazole-induced hypothyroidism reduced zinc levels. In the study by Kuriyama *et al.*[22], red blood cell zinc concentration was significantly lower in transient hypothyroidism patients than in permanent hypothyroidism patients. The low zinc levels we obtained in our study are in harmony with the results of the aforementioned researchers. Serum selenium levels in the hypothyroidism group (group 3) were lower than those in the other two groups. Similar findings have been reported by other researchers[23]. Selenium is a nutritive trace element required for regulation of thyroid hormones, redox state of vitamin C and functioning of other molecules, thanks to its protective effect against oxidative stress[24]. Selenium accumulates as selenocysteine in the active fragment of the wide domain of proteins. Until today, 15 selenoproteins have been purified or cloned, allowing the identification of their biological functions[24]. These are 4 glutathione peroxidase enzymes representing the major class of selenoproteins that are functionally important[24]. Among the selenoproteins, iodothyronine deiodinases catalyze the conversion of inactive T_3 to 3' diiodothyronine and pro-hormone thyroxin (T_4) to active thyroid hormone 3,3'5 triiodothyronine[25]. As a result, selenium is very important in the modulation of the regulatory role of thyroid hormones in the metabolism[26]. According to the report by Liu *et al.*[14], the levels of selenium change markedly in various thyroid malfunctions. The levels of selenium in thyroid tissue of patients with thyroid cancer were shown to be significantly inhibited[10]. It has been reported that animals with selenium deficiency had lower thyroid hormone concentrations[27], or that selenium values dropped in thyroid malfunctions[28]. Low selenium levels we obtained in the present study are consistent with the results of researchers who report altered selenium levels in impaired thyroid functioning.

Reports indicate that calcium levels remain unchanged or decrease in hypothyroidism[29,30]. However, hypocalcemia provoked by EDTA infusion to hypothyroidism patients is deeper at long run[31]. The sensitivity of bone and kidney to parathormone (PTH) decreases in hypothyroidism[31]. Therefore, the increased production of active vitamin D and PTH in hypothyroidism does not cause hypercalcemia due to the decline in tissue sensitivity[29-31]. In our study, we also found significant decreases in serum calcium levels of the hypothyroidism group. In their study, O'Dell *et* *al.*[32] demonstrated that zinc deficiency in the body resulted in insufficient calcium absorption. It has been reported that 1,25 dihydroxycholecalciferol levels in circulation dropped in zinc deficiency, or alternatively that zinc supplementation stimulated the synthesis of 1,25 dihydroxycholecalciferol[33]. Low calcium levels we obtained in the hypothyroidism group seem to have resulted from the decrease in zinc levels.

In a study including thyroid cancer patients, preoperative magnesium values of the patients were not different from those in the controls, but declined significantly after the operation[13]. Dolev *et al.*[15] found a decline in urinary discharge and clearance of magnesium in hypothyroidism patients. Magnesium levels declined in the liver and brain tissues, remained unchanged in the renal tissue, and increased in the heart tissue of rats with induced hypothyroidism[34]. However, Erdal *et al.*[23] report that basal manganese levels are reduced in subclinical hypothyroidism. Results of studies on how magnesium values are affected in hypothyroidism seem contradictory, and are focused on changes in tissues. In our study, serum magnesium values did not differ among the groups. The result of our study regarding this parameter indicates that serum magnesium values do not change in hypothyroidism.

The hypothyroidism group (group 3) had higher chromium, copper, iron and phosphorus levels as compared with other groups in our study. It has been argued that copper metabolism is impaired in thyroid diseases[35]. Copper concentration in the renal tissue was shown to decrease in rats with induced hypothyroidism[34]. Similarly, it has been reported that copper levels increased in patients with thyroid cancer[10], and that iodine deficiency significantly altered copper levels in the rat brain tissue[14]. But, Alturfan *et al.*[21] determined that copper levels were decreased in methimazole-induced hypothyroidism. The high copper levels we obtained in our study uphold the findings of researchers who have argued that copper metabolism is impaired in thyroid malfunctions. Iron levels in rat tissues change in iodine deficiency[14]. Similar results were recorded on postoperative measurements in patients with thyroid cancer[13]. It has been reported that iron supplementation reduced hyperthyroidism in rats with induced hyperthyroidism and inhibited plasma ferritin levels[36]. However, Erdal *et al.*[23] found that basal iron levels were decreased in subclinical hypothyroidism. The high iron levels we found in our study indicate that this metal is influenced by impairments in thyroid metabolism. We could not determine antioxidant molecules such as reduced glutathione (GSH) in the present study. However, we determined GSH levels in our previous study in experimental hypothyroidism[37]. Thus, it may be suggested that copper and zinc act as antioxidant molecules and exert their effects in an indirect manner in experimental hypothyroidism. We could not find any result with which we could compare increased chromium and phosphorus levels we obtained in the hypothyroidism group (group 3). However, the findings we obtained demonstrate that these elements are at least affected by hypothyroidism. The higher chromium, copper, iron and phosphorus levels we found in the hypothyroidism group may also be associated with low zinc levels recorded in the same group. McDonald and Keen[38] noted the presence of an interaction between dietary zinc and other elements, and argued that excessive iron intake in particular might lead to zinc deficiency. The results of our study suggest an inverse correlation between iron and zinc. A balance was noted between zinc, an important trace element, and copper, iron and phosphorus[31-33]. It has been reported that high-dose zinc could impair copper-iron absorption[41], and also that high-dose phosphorus-iron-copper might impair zinc absorption[42,43]. The high copper, iron and phosphorus values we obtained in this study could be considered to result from decreased zinc levels.

The results of this study indicate that hypothyroidism brings about changes in the levels of some elements in rats. These changes may be associated with decreased zinc levels in hypothyroidism.

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Sažetak

ODNOS SERUMSKIH RAZINA KALCIJA, SELENA, MAGNEZIJA, FOSFORA, KROMA, BAKRA I ŽELJEZA PREMA CINKU KOD ŠTAKORA S IZAZVANIM HIPOTIROIDIZMOM

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Odnos između hormona štitnjače i cinka veoma je važan. Nalaz niskih razina cinka kod hipotiroidizma i visokih razina kod hipertiroidizma značajan je dokaz ovoga odnosa. Cilj ovoga istraživanja bio je ispitati promjene serumskih razina nekih elemenata i njihov odnos prema cinku kod štakora s hipotiroidizmom. Trideset odraslih Sprague-Dawley štakora mužjaka podijeljeno je u tri jednake skupine: 1. kontrolna skupina; 2. skupina s lažnim hipotiroidizmom, s dodatkom 10 mg/kg fiziološkog seruma i.p. kroz 4 tjedna; 3. skupina s hipotiroidizmom, s dodatkom 10 mg/kg propiltiouracila i.p. kroz 4 tjedna. Uzorci krvi prikupljeni su dekapitacijom, a serumske razine kalcija, fosfora, kroma, bakra, željeza, magnezija, selena i cinka analizirane su primjenom uređaja za atomsku emisiju. Skupina 3. imala je niže razine kalcija, selena i cinka te više razine kroma, bakra, željeza i fosfora ($p<0{,}01$ sve) u odnosu na skupine 1. i 2. Ovi parametri nisu se razlikovali među skupinama 1. i 2. Rezultati dobiveni u ovom ispitivanju ukazuju na to da hipotiroidizam dovodi do promjena u razinama nekih elemenata kod štakora. Ove promjene mogle bi biti udružene sa sniženim razinama cinka u hipotiroidizmu.

Ključne riječi: *Selen; Bakar; Cink; Željezo; Hipotiroidizam; Štakor*