Influence of thyroid status on the content of essential chemical elements in the body of laboratory animals

S V Notova¹, E V Kiyaeva¹, S V Miroshnikov¹, T V Kazakova¹

¹Federal Research Centre of Biological Systems and Agrotechnologies RAS, Orenburg, 460000, Russia
E-mail: elena_sap@mail.ru

Abstract. The purpose of this study was to identify the characteristics of the redistribution of chemical elements in various biosubstrates when modeling thyrotoxicosis and hypothyroidism in animals. Male Wistar rats were the object of the study. Animals of the first experimental group were intraperitoneally injected with L-thyroxine to simulate the state of experimental thyrotoxicosis. Animals of the second experimental group were injected merkazolila to simulate the status of experimental hypothyroidism. The third group was the control group. The obtained data demonstrated the effect of thyroid status on mineral metabolism. The greatest changes in the elemental status were found in the thyroid gland: a high content was found in hypothyroidism Cr (p<0.05), V (p<0.05), Co, Fe, As, Ni, Mn, Se, Zn and lower values I (p<0.05) and Si (p<0.05); with hyperthyroidism – a higher content of Co (p<0.01), Ni (p<0.05), Cu (p<0.05), Zn (p<0.05), Cr (p<0.05), Li, V, Mn and lower content of Si (p<0.05). When comparing the experimental groups, statistically significant differences were revealed: hyperthyroidism was accompanied by accumulation of Cu, Zn, I in the thyroid gland; hypothyroidism - As, Se and V. Statistically significant lower values of Cr, Cu, Ni, Se, Si, V, Zn and a tendency to lower As, I, Fe and Mn values were recorded in the bone tissue of animals from the experimental group I, in animals of experimental group II a higher content of almost all the studied microelements was observed, however, statistically significant differences were obtained only in terms of As (p<0.05) and Ni (p<0.05). In the hair of animals, when modeling hyperthyroidism and hypothyroidism, higher values of Fe, Se, Si, V, Cr were observed as compared to the control.

1. Introduction
Thyroid hormones have a wide range of physiological effects and control metabolism, total energy consumption, oxygen consumption, and adaptive capabilities [1, 2].

Synthesis, secretion, metabolism and the activity of thyroid hormones in tissues depend on the balance of a number of essential trace elements, which together contribute to an adequate hormonal status of the thyroid gland [5, 6]. So in the literature there are experimental and clinical data confirming the hypothesis of the goiter-induced effect of zinc deficiency – an important component of many metabolic processes. The WHO manual on iodine-deficient conditions does not exclude the effect of iron on the synthesis of thyroid hormones and suggests the decrease in iodine absorption with a deficiency of this element [7]. A number of studies have shown the effectiveness of prescribing micronutrient preparations in patients with various forms of thyroid status disorders [8]. However, most studies are related to the assessment of the elemental composition of blood serum only for various diseases and disorders of the functioning of the thyroid gland [9].

Recently there appear works devoted to the study of the influence of the functioning of the thyroid gland on metabolism of individual elements. So in the work of M.A. Paulazo et al. data is provided on the metabolism of zinc in hypothyroidism [10]. It is known that thyroid hormones play an important role
in the development of the skeleton and maintaining bone health \([11, 12, 13]\). However, most studies are devoted to assessing the content of the main structural macroelements of inert tissue, calcium and phosphorus, while trace elements are also involved in bone remodeling. This justifies the choice of this biosubstrate to assess the influence of the thyroid status on the content of essential elements.

Of particular scientific interest are the features of the content and distribution of chemical elements in various tissues of the body under conditions of change or violation of thyroid status, as this may help to clarify some pathogenetic aspects of clinical syndromes such as thyrotoxicosis and hypothyroidism that are very common in the population.

The purpose of this study was to study the influence of the thyroid status on the content of essential chemical elements in the organism of laboratory animals and to identify the characteristics of their redistribution in various biosubstrates.

2. Materials and methods

2.1 Object of study
Male Wistar rats \((n=90)\) weighing from 180 to 200 grams. Experimental studies and maintenance of animals were performed in accordance with the instructions and recommendations of the Russian Regulations, 1987 (Order No.755 on 12.08.1977 the USSR Ministry of Health) and "The Guide for Care and Use of Laboratory Animals ("The National Academy Press" 1996). In conducting the research, efforts have been made to minimize sufferings of animals.

2.2 Experimental design
Physiological studies were carried out in vivarium conditions of the Central Clinical Hospital of the BST RAS. Experimental animals were divided into three groups depending on the function of the thyroid gland.

L-thyroxine was injected intraperitoneally daily for 15 days into animals of experimental group I \((n=30)\) at the rate of 200 \(\mu\)g per kg of body weight to simulate the state of experimental thyrotoxicosis [14]. Animals of the experimental group II \((n=30)\) daily for 15 days were injected intraperitoneally mercazolil at the rate of 1 mg per 100 g of body weight to simulate the state of experimental hypothyroidism [15]. The third group \((n=30)\) was the control group. A threefold study of the levels of TSH and free T4 serum confirmed the condition of manifest thyrotoxicosis and hypothyroidism.

Evaluation of the functional state of laboratory animals by the integral indicator, including the study of the dynamics of body weight, the volume of daily food and fluid intake, changes in external signs was carried out daily.

2.3 Equipment and hardware
Analytical studies were carried out in the laboratory of ANO "Center for Biotic Medicine" (Moscow), using ICP-AES instruments (Optima 2000DV, PerkinElmer Corp.), ICP-MS (ELAN 9000, Perkin Elmer Corp.).

2.4 Statistical processing
Processing of the obtained data was carried out by the methods of variation statistics using the statistical package StatSoft STATISTICA 6.1.478. The storage of the obtained research results and the initial processing of the material were carried out in the original database "Microsoft Excel 2010". The compliance of the obtained data with the normal distribution law was checked using the Kolmogorov's criterion of consent. The hypothesis of data belonging to the normal distribution was rejected in all cases with a probability of 95 %, which justified the use of non-parametric procedures for processing statistical aggregates (Mann-Whitney U-test). The data obtained are presented in the form of quarters 25-75 (Q1-Q3).

3. Discussion of the results
Evaluation of the functional state of the thyroid gland showed that in the first experimental group throughout the experiment the state of manifest thyrotoxicosis remained: the level of TSH - 0.04 μMU / l, free T4 - from 33.5 to 38.9 pmol / l. The state of increased thyroid status was indicated by increased excitability, ruffled hair, pelvic muscle hypotrophy, exophthalmos, changes in body weight and rectal temperature. By the end of the experiment, the rectal temperature of animals of the first experimental group exceeded the level of control by 1.6 ± 0.05 ° C (p<0.05); body weight decreased by 9% from baseline (p<0.05). These data confirm the modeling of a hypermetabolic state in animals of this group, associated with increased energy expenditures [16]. In animals of the second experimental group, the symptoms of hypothyroidism differed – lack of appetite, low mobility, drowsiness, loss of hair from the side surfaces of the body, weight gain by 12% (p<0.05). Weight gain in the control group was 5 % (p<0.05). The level of TSH in this group had the highest values (0.25 μIU / l), and the free T4 – the lowest (4.9 pmol / l).

In the control group throughout the experiment, the level of hormones corresponded to the physiological norm (TSH = 0.12 μME / L; T4 = 11.2 pmol / L).

Considering the change in the content of chemical elements in the thyroid gland, bone tissue and hair of laboratory animals with different thyroid status, a number of features can be observed. As one would expect in this experiment, the greatest changes in the elemental status are observed in the thyroid gland (Table 1).

Table 1. The content of chemical elements in the thyroid gland of laboratory animals

| Element | Control Group Med (Q1-Q3) | I Group Med (Q1-Q3) | II Group Med (Q1-Q3) |
|---------|---------------------------|---------------------|----------------------|
| Co      | 0.015 (0.014-0.019)       | 0.042 (0.040-0.042) | 0.029 (0.029-0.032) |
| Cr      | 0.19 (0.165-0.205)        | 0.56 (0.47-0.81)    | 0.52 (0.47-0.54)    |
| Cu      | 2.79 (2.6-3.15)           | 4.31 (3.81-4.51)    | 2.88 (2.74-3.0)    |
| Fe      | 66.8 (62.9-88.4)          | 64.2 (60.4-68.4)    | 85.2 (76.2-93.0)   |
| As      | 0.051 (0.047-0.056)       | 0.042 (0.031-0.047) | 0.087 (0.078-0.108) |
| I       | 82.2 (79.7-104.4)         | 61.8 (57.7-71.3)    | 13.8 (10.7-14.9)   |
| Li      | 0.001 (0.0009-0.0012)     | 0.0012 (0.0009-0.00145) | 0.0011 (0.0009-0.0012) |
| Ni      | 0.33 (0.255-0.37)         | 0.56 (0.51-0.61)    | 0.4 (0.39-0.41)    |
| Se      | 0.53 (0.43-0.58)          | 0.5 (0.49-0.50)     | 0.837 (0.763-0.878) |
| Si      | 3.45 (2.74-4.32)          | 0.61 (0.52-0.75)    | 0.097 (0.09-0.101) |
| V       | 0.0002 (0.0002-0.00035)   | 0.0019 (0.0014-0.0026) | 0.021 (0.018-0.029) |
| Zn      | 36.7 (32.6-39.7)          | 51.1 (50.5-51.9)    | 43.8 (41.8-44.8)   |
| Mn      | 0.89 (0.81-0.98)          | 1.02 (0.68-1.29)    | 0.97 (0.62-1.38)   |

Data presented as Median (25–75 percentiles).

a Significant difference compared with control at p <0.05.

b Significant difference compared with group I at p <0.05.

The state of hyperthyroidism was accompanied by a higher content in the thyroid gland of most elements: Co (p<0.01), Ni (p<0.05), Cu (p<0.05), Zn (p<0.05), Cr (p<0.05), Li, V, Mn and lower Si content (p<0.05).

When modeling hypofunction in the thyroid tissue, a higher content of Cr (p<0.05), V (p<0.05), Co, Fe, As, Ni, Mn, Se, Zn and a lower content of I (p< 0.05) and Si (p<0.05) were observed.

Thus, regardless of the nature of the thyroid status in the experimental groups, compared with the control group, there was a “unidirectional” vector of changes in the content of most of the studied elements with the exception of Se. When comparing the experimental groups, statistically significant differences were also revealed: hyperthyroidism was accompanied by accumulation of Cu, Zn, I in the thyroid gland; hypothyroidism – As, Se and V.
Compared to the control group, statistically significant lower Cr, Cu, Ni, Se, Si, V, Zn contents and a tendency towards lower As, I, Fe, and Mn values were recorded in the bone tissue of animals in the experimental group I (Table 2). Hyperthyroidism is known to cause osteoporosis and an increased risk of fracture. Such complications arise from an imbalance between the resorption rate and bone formation, resulting in a loss of approximately 10% of the bone during the remodeling cycle [17].

In animals of the second experimental group, a higher content in the bone tissue of almost all the studied trace elements was observed, however, statistically significant differences were obtained only in terms of As (p<0.05) and Ni (p<0.05).

### Table 2. The content of chemical elements in the bone tissue of laboratory animals

|        | Control Group | I Group | II Group |
|--------|---------------|---------|---------|
|        | Med (Q1-Q3)   | Med (Q1-Q3) | Med (Q1-Q3) |
| Co     | 0.06 (0.064-0.065) | 0.062 (0.058-0.065) | 0.069 (0.067-0.07) |
| Cr     | 0.41-(0.41-0.41) | 0.37 (0.36-0.40) a | 0.44 (0.42-0.45) |
| Cu     | 1.7 (1.68-1.725) | 1.16 (1.13-1.19) a | 1.64 (1.58-1.67) a |
| Fe     | 41.3 (40.7-43.25) | 37.6 (37.3-37.8) | 40.4 (38.7-42.4) |
| As     | 0.04 (0.039-0.041) | 0.038 (0.032-0.04) | 0.09 (0.08-0.11) ab |
| I      | 0.16 (0.13-0.18) | 0.1 (0.1-0.16) | 0.18 (0.17-0.185) b |
| Li     | 0.034 (0.017-0.037) | 0.027 (0.025-0.028) | 0.036 (0.035-0.037) |
| Mn     | 0.59 (0.54-0.67) | 0.56 (0.49-0.65) | 0.71 (0.56-1.11) |
| Ni     | 0.57 (0.57-0.571) | 0.101 (0.099-0.101) a | 0.8 (0.74-0.80) a |
| Se     | 1.09 (0.96-1.36) | 0.72 (0.70-0.73) a | 1.51 (1.34-1.55) |
| Si     | 31.7 (31.6-32.1) | 23.4 (21.3-26.3) a | 31.5 (30.5-32.7) |
| V      | 0.004 (0.0039-0.004) | 0.003 (0.0029-0.003) a | 0.0042 (0.0039-0.004) |
| Zn     | 49.4 (47.5-49.7) | 41.7 (40.9-43.9) a | 57.1 (51.4-59.3) |

Data presented as Median (25–75 percentiles).

a Significant difference compared with control at p <0.05.
b Significant difference compared with group I at p <0.05.

Our data confirm the known fact of slowing the formation of bone tissue in hypothyroidism due to an increase in mineralization and bone mass without changing its volume [18].

In the hair of animals when modeling hyperthyroidism, higher values of the content of almost all essential elements were observed (Table 3). The largest statistically significant difference with the control was found for Fe, Ni, Se, Si, V, Cr, the content of which in hyperthyroidism was 3.7, 2.6, 2.1, 1.5, 2.6 and 1.5 times higher, respectively.

In the state of hypothyroidism, similar changes were observed in animal hair: the content of Cr, Fe, Se, Si, and V was 2.7, 2.5, 9, 1.9, and 7 times higher than in the control.

### Table 3. The content of chemical elements in the hair of laboratory animals

|        | Control Group | I Group | II Group |
|--------|---------------|---------|---------|
|        | Med (Q1-Q3)   | Med (Q1-Q3) | Med (Q1-Q3) |
| Co     | 0.056 (0.053-0.061) | 0.06 (0.027-0.099) | 0.03 (0.027-0.035) |
| Cr     | 1.85 (1.42-2.0) | 2.75 (2.51-2.88) a | 4.94 (4.05-5.82) a |
| Cu     | 10.4 (9.23-11.05) | 11.8 (11.6-11.9) | 11.7 (11.4-11.9) |
| Fe     | 21.3 (16.9-27.7) | 77.8 (52.0-80.0) a | 53.8 (44.8-60.2) a |
| As     | 0.039 (0.031-0.045) | 0.051 (0.044-0.057) | 0.061 (0.0135-0.010) |
| I      | 1.30 (0.87-1.70) | 1.63 (1.58-1.67) a | 1.40 (1.16-1.68) |
There is not only a dependence of the thyroid function on the
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erum zinc metabolism [34].
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background of a decrease in bone tissue, which confirms the literature data that states that hyperthyroidism has a significant effect on Cu metabolism [34].
A number of studies have shown changes in the serum of patients with various thyroid diseases levels of Co, V and several other elements, but at present there is insufficient data on the biological function of these elements in diseases of the thyroid gland [35].

There is a large amount of evidence in the literature about the hypothyroid effects of Li [36, 37] associated with its effect on iodine metabolism, thyroglobulin structure, thyroxin secretion, and T4 to T3 conversion [38, 39, 40]. In our study, no reverse effect was found: the content of Li in the thyroid gland, bone tissue, and animal hair of the experimental groups was practically the same as of the control group.

From the point of view of non-invasive diagnosis, it is interesting to identify the relationship between the content of specific elements in the hair, thyroid and bone tissue. As shown by correlation analysis, a limited number of reliable relationships was found between the content of identical elements in hair and thyroid tissue, in particular, in the experimental groups a correlation was found for Cr (r = 0.35), I (r = –0.41), V (r = 0.37) and Si (r = –0.46), and for hypothyroidism, and for Se (r = 0.45). When the euthyroid state the relationship was not detected.

4. Conclusion
The obtained data clearly demonstrated the effect of the thyroid status on mineral metabolism. The greatest effect on the content of essential and conditionally essential trace elements had experimental hypothyroidism. At the same time, along with the “expected” changes, a number of elements were revealed, the level of which was not previously associated with thyroid status.

Different thyroid status influenced the redistribution of chemical elements in animal biosubstrates. The most pronounced changes in the elemental composition, as expected, were recorded in the thyroid gland. Moreover, the dynamics of the content of elements compared with the control group was “unidirectional” in experimental groups and was manifested by a higher content of almost all trace elements. Minimal changes were recorded in the bone tissue, however, the nature of the changes clearly indicates the effect of the thyroid status on the remodeling processes. If thyroid status is violated, the content of Cr, I, V, and Si and Se in the thyroid gland can be indirectly judged by the content of these elements in animal hair.

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