ABSTRACT

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The dissertation thesis
“Bioelement status of children with thyromegaly in the Western region of the Republic of Kazakhstan”

submitted for the degree of Doctor of Philosophy (PhD) by the specialty 6D110100 – “Medicine”

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Relevance. The stability of the elemental composition of the human body is one of the conditions for its normal functioning (Avtsyn A.P., Zhavoronkov A.A., 1991). The trace element profile of the living environment is reflected in the bioelement status of the human body. Imbalance of bioelements, their deficiency or excess in the body leads to the formation of endemic diseases (Kubasova E.D., 2007). One of the global elementosis is iodine deficiency (Bailey R.L. et al., 2015). Despite all efforts to eliminate iodine-deficient diseases in the world, according to the World Health Organization (WHO), 29.8% of school-age children still have insufficient iodine intake (Zimmermann M.B., 2013). Iodine deficiency, an important component of thyroid hormones, can lead to goiter, hypothyroidism, infant and perinatal mortality, spontaneous miscarriage, congenital abnormalities. Adequate intake of iodine is crucial for the normal growth and development of the nervous system of a developing organism, the formation of a child’s intelligence (Pearce E.N., 2014; Obican S.G., 2012).

The state policy for preventing iodine deficiency disorders is implemented in the Republic of Kazakhstan, and in 2010 the country was certified as having eliminated iodine deficiency through universal salt iodization (IDD NEWSLETTER, 2011). However, in the Western region of the Republic of Kazakhstan (RK) there is a steady increase in thyroid disease in children and adults (Kudabayeva Kh.I. et al., 2013).

Despite the recognized leading role of iodine deficiency, today, the enlargement of the thyroid gland is considered as a manifestation of human thyroid maladjustment reactions to a complex of adverse climatic and socio-environmental factors (Gorbachev A.L., 2013). Thyromegaly has a mixed genesis and is the result of a complex interaction of endo- and exogenous factors. Under the influence of natural and anthropotechnogenic strumogens, the physiological mechanism of iodine utilization and the realization of its biological action is disturbed. In the genesis of goiter endemia, the role of “nonspecific” strumogens is defined, which include the disturbed microelement profile of the environment. An excess or deficiency of some essential bioelements controlling the synthesis of iodinated hormones can block the absorption of iodine, disrupt the synthesis and metabolism of thyroid hormones, which includes structural mechanisms for enhancing the function of the thyroid gland (Kubasova E.D., 2009).

The environmental distress of the regions of Western Kazakhstan in some cases leads to significant changes in the “microelement portrait” of the population (Dzhaugasheva K.K., Skalnaya M.G., 2004). It has been proven that, under the conditions of a pronounced anthropogenic effect of chemical factors, the imbalance of trace elements manifests itself to a greater degree (Kurganov V.Ye., 2015). The high frequency of goiter in the region revealed by the results of a pilot study (Kudabayeva Kh.I. et al., 2013) does not exclude the participation of an imbalance of bioelements in its development. It is known that the extraction and use of resources causes numerous environmental problems associated with environmental pollution with oil products, heavy metals, compounds of carbon, sulfur, nitrogen oxides and other substances. However, it is known that the function of the thyroid
gland responds subtly to natural and man-made factors, therefore the thyroid gland is often considered as a marker of the region’s ecological distress.

**Aim of the study:** to study the severity of goiter endemia in the Western region of the Republic of Kazakhstan on the example of the Aktobe, West Kazakhstan, Atyrau, Mangystau regions and to assess the effect of bioelements on its formation.

**Objectives of the study:**
1. To assess the severity of goiter endemia by the prevalence of thyromegaly among schoolchildren in Western Kazakhstan.
2. To study the features of the bioelement status of children from various regions of Western Kazakhstan.
3. To study the effect of bioelements on the development of thyromegaly.

**The object of the research** was 6493 school-age children (6-12 years old), permanently residing in Western Kazakhstan.

**The subject of the study** was physiological parameters (body length, body weight, thyroid volume), children's biological environments: hair - 25 chemical elements (aluminum (Al), arsenic (As), calcium (Ca), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), iodine (I), potassium (K), lithium (Li), magnesium (Mg), manganese (Mn), sodium (Na), nickel (Ni), phosphorus (P), lead (Pb), selenium (Se), silicon (Si), strontium (Sn), boron (B), beryllium (Be), vanadium (V), mercury (Hg), zinc (Zn).

**Scientific novelty of the research:**
- for the first time, a large-scale study of the prevalence and intensity of goiter endemia was conducted on the territory of four regions of Western Kazakhstan using the diagnostic methods recommended by WHO.
- for the first time, a large-scale assessment of the bioelement status of children aged 6-12 years old was carried out in Western Kazakhstan.
- for the first time, the features of the bioelement status and the relationship between the volume of the thyroid gland and the content of bioelements in the hair of children in the Aktobe, Atyrau, West Kazakhstan (WKR), and Mangystau regions were established.

**The practical significance of the dissertation research**
1. The results of the study allow us to objectively assess the extent of the prevalence of goiter endemia in Western Kazakhstan. The determination of the volume of the thyroid gland in children of primary school age in all regions of Western Kazakhstan revealed an excess of the normative values recommended by WHO. The obtained data can be used to develop reference values of the volume of the thyroid gland for the region under study.
2. The results of the bioelement status study can be used for scientifically-based planning of the bioelement correction directions in order to prevent goiter endemia; to serve as a basis for organizing additional measures to minimize the polluting effects of anthropotechnogenic factors, taking into account the environmental features of various regions.
3. The results of the study of the prevalence of deficiency of elements in the children's population of the region can be used to develop recommendations for the prevention of combined micronutrient deficiency.

4. The research results are used in the educational process at the Department of Internal Diseases No. 1 of the WKMOSMU, implemented in Practical health care (Public health Department of Aktobe region, SCE on REJ “City Polyclinic №5”, Clinic of Family Medicine of WKMOSMU), Mangystau (SCE on REJ “Aktau city polyclinic №2”), Atyrau (SCE on REJ "Atyrau city polyclinic №2") regions.

**Provisions for the defense:**

1. In the Western region of Kazakhstan there is a pronounced goiter endemia. At the same time, the prevalence of thyromegaly in children of school age, according to WHO criteria, corresponds to severe endemia.

2. The elemental status of the child population of Western Kazakhstan is characterized by a deficiency of selenium, cobalt and excessive accumulation of silicon and lithium in the hair.

3. Tense goiter endemia in the region is caused by the goiter effect of the imbalance of bioelements – boron, vanadium, silicon, which was intensely manifested against the background of the population deficiency of selenium, cobalt and excess lithium, silicon.

**Personal contribution of the author**

The data collection was carried out by the staff of the Department of Internal Diseases No. 1 with the direct participation of the doctoral student and the supervisor during epidemiological visits as part of a research group of research work with grant funding from the Ministry of Education and Science of the Republic of Kazakhstan "Epidemiology of endemic goiter in the Western region of Kazakhstan and the development of recommendations for the prevention of iodine deficiency conditions” in the region of Western Kazakhstan. All the main sections of the thesis (data collection, processing and analysis of the primary material, interpretation of the results and their discussion, formulation of the main provisions and conclusions), hair sampling for analysis were performed by the author herself.

**Approbation of work**

The main provisions of the thesis were presented at the International Scientific and Practical Conference "Innovative Technologies for the Protection of Children's Health and Reproductive Health" (Aktobe, 2016); International Conference of the Caspian Sea littoral states (Astrakhan, Russia, 2016); International Scientific and Practical Conference of Students and Young Scientists "Science and Medicine: A Modern View of Youth" (Almaty, 2017); the 11th International Scientific and Practical Conference "Achievements of Basic Sciences - the Basis for the Formation of Modern Medicine" (Astrakhan, Russia, 2018); the 16th International Symposium on Trace Elements in Man and Animals (TEMA-16) (Saint-Petersburg, Russia, 2017).

**Publications on the dissertation topic.** 12 papers were published on the topic of the thesis, of which 1 - in the Journal of Elementology, indexed in the Web
of Science information database (IF = 0.684 in 2017); 2 - in the journal, indexed in the Scopus information database “Georgian medical news” (SGR = 0.14 in 2017); 3 articles - in publications recommended by the Committee on the Control of Education and Science of the Republic of Kazakhstan; 2 theses - in collections of the International scientific and practical conferences (foreign); 1 thesis and 1 article were published in the materials of the International scientific conferences. 2 certificates of state registration of rights to the object of copyright were received.

Materials and research methods

The study was conducted in the framework of research with grant financing of the MES RK "Epidemiology of endemic goiter in the Western region of Kazakhstan and the development of recommendations for the prevention of iodine deficiency conditions" (state registration number 013RK00439).

Study design is a simultaneous cross-sectional research. The work was approved by the local ethical committee of the West Kazakhstan Marat Ospanov State Medical University (protocol No. 11 from 30.11.2015). The research work was carried out in accordance with the principles of the Helsinki Declaration and subsequent amendments. Informed consents were obtained from the parents / legal representatives of the children.

Scientific research was conducted on the territory of Western Kazakhstan in the framework of cluster analysis on the study of iodine deficiency diseases and monitoring of their elimination. In accordance with the recommendations of WHO, a selection of survey sites was conducted using a probability proportional to size sampling (PPS) and simple random sampling. The systematic sampling method selected 30 clusters from the general population. The total population of each region was divided by 30, and the sampling interval (k) was obtained. The starting point of the survey was chosen by selecting a random number in the range from 1 to k. The selection of schools within the cluster is carried out using a table of random numbers. The children of secondary schools who reside in the area and meet the inclusion criteria were examined by a continuous method. The pilot study showed an estimated prevalence of goiter as 50%, which made it possible to calculate a sample of 83 pupils from each school (statistically significant, for a 95% confidence interval).

Inclusion criteria: age of children (6-12 years); written informed consent before inclusion in the study.

Exclusion criteria: children with severe somatic diseases; thyroid disease in history. Exclusion criteria were determined by the available medical records, interviews with parents, teachers, subjects.

The children 6-12 years of age were examined due to their high susceptibility to iodine deficiency and accessibility for study (WHO, 2007).

All data (gender, age, body weight, body length) were recorded in the questionnaire and are presented in Table 1. The height and weight of the children were determined by the standard method.

Determination of the size of the thyroid gland by the method of ultrasonography. Thyroid sonography was carried out using a portable scanner ALOKA SSD-500 with a sensor of 7.5 MHz (made in Japan). The measurements
were carried out in the longitudinal and transverse planes for the right and left lobes. The volume of each lobe of the thyroid gland was calculated by the formula proposed by Brunn J., 1981:

\[ V \text{ (ml)} = 0.479 \times d \times w \times l \text{ (cm)}, \]

where \( V \text{ (ml)} \) is the volume of the thyroid lobe (ml); \( d \) is the thickness of the thyroid lobe (cm); \( w \) is the width of the lobe of the thyroid gland (cm); \( l \) is the length of the lobe of the thyroid gland (cm); 0.479 is the ellipsoidal correction factor.

The thyroid volume included the volume of its two lobes: right and left, excluding the volume of the isthmus.

The surface area of the body was determined by the nomogram (Graford, Terry and Rourke from Fanconi G., Walgren A.: Lehbuch der Padiatrie, 3 aufl. Basel, Shwabe, 1954). The data obtained were assessed relative to the BSA and gender according to the protocols recommended by WHO (2007). All cases of excess of the actual volume of the thyroid gland above the upper limit of normal (97 percentile) were taken as the frequency of thyromegaly in the population.

**The study of the bioelement composition of the hair.** In order to assess the bioelement status, macro- and microelement hair analysis was performed in 498 children. For the microelement analysis of hair by the method of simple random sampling, the examined children were selected in two groups: with thyromegalia and without thyromegaly. The content of twenty-five chemical elements was estimated: Al, As, B, Be, Ca, Cd, Co, Cr, Cu, Fe, I, K, Li, Mn, Mg, Na, Ni, P, Pb, Se, Si, Sn, V, Hg, Zn. According to Green S.B. (1991), for carrying out regression analysis, the sample should be 10-20 times the increased number of analyzed variables. In our case, the sample should be 250-500 people.

The object of research in our work was the hair. Possessing a number of advantages as a biological substrate, hair is distinguished by durability and does not undergo biological changes. Hair, unlike blood or urine, is much less dependent on systems that regulate homeostasis. A hair sample can be obtained without injuring the patient, and the storage and transportation of the material does not require special equipment: the hair does not deteriorate and can be kept without time limits.

Hair samples were obtained by trimming with clean stainless steel scissors from 3-5 sections of the back of the head in an amount of at least 0.1 g. For elemental hair analysis, proximal parts of the strands 3-4 cm long were used. Samples were placed in envelopes with identification records. At the same time, age, gender, hair color, place of permanent residence was indicated in the direction. Hair samples obtained from children were sent for analysis to the laboratory of ANO "Center for Biotic Medicine" (Moscow, Russia). ANO "Center for Biotic Medicine" is an ISO Europe certified laboratory; certified by the Quality Management System that complies with the requirements of the international standard ISO 9001: 2008. (Registration information: OGRN 1027700072157 of July 29, 2002).

Analytical studies of the elemental composition of hair were performed by mass spectrometry with inductively coupled plasma (MS-ICP) and atomic emission spectrometry with inductively-coupled plasma (AES-ICP). Samples were
analyzed on an Optima 2000 DV atomic emission spectrometer (Perkin Elmer, United States) and a Nexion 300D quadripole mass spectrometer (Perkin Elmer, United States).

All hair samples were subjected to laboratory sample preparation according to the requirements of the IAEA. Hair samples were treated with acetone (OSC) for degreasing and removal of impurities for 10-15 minutes and washed three times with distilled water. Then the samples were dried in a drying cabinet at a temperature of 60ºC until air-dry. A weight of dried and crushed hair weighing 0.1 g was taken on an analytical balance. The resulting weight of hair was placed in a plastic graduated test tube and 1 ml of nitric acid was added. The sample was kept in a test tube in a water bath for 1 hour. Then the tube was cooled to room temperature, and the volume of the solution was adjusted with bidistilled water to 10 ml. The control sample was prepared without hair, but in compliance with all the above steps. The standard sample used was the GBW09101 “Human hair” certified standard hair sample, issued by the Shanghai Nuclear Research Institute (Shanghai Institute of Nuclear Research, PR China). The system was calibrated using the Universal Data Acquisition Standards Kit (PerkinElmer Inc., USA). Internal online standardization was performed using the Yttrium-89 isotope solution obtained from the Yttrium (Y) Pure Single-Element Standard (PerkinElmer Inc., USA).

Determination of the content of chemical elements in the hair using ICP-AES and ICP-MS methods allows a comprehensive assessment of the impact of environmental, hygienic and physiological factors on the body in children. The technique is characterized by high sensitivity, informative, performance.

**Statistical analysis**

The obtained data were processed using SPSS 25 software (SPSS Inc, Chicago, IL, USA), Statistica10 (StatSoftInc., USA). The distribution of data was assessed using Kolmogorov-Smirnov criteria. For descriptive statistics of quantitative variables, the mean value (M), standard deviation (SD), and in the case of a distribution other than the normal median (Me) and 25 and 75 percentiles (Me (q25 – q75)) were used. Frequencies (in%) with 95% confidence intervals were used to describe qualitative data.

Student’s criterion was used to assess the statistical significance of differences in values with a normal distribution. In the case of non-compliance with the law of normal distribution, to assess the differences in two groups - the Mann-Whitney U test, in three or more - the Kruskal-Wallis H-test was applied. Categorical data were analyzed using Pearson's chi-square test. Correlation analysis was performed using the Spearman coefficient for rank correlation.

The relationship between the volume of the thyroid gland and the content of bioelements in the hair of the subjects was assessed using multiple linear regression analysis, in which the total thyroid volume was used as a dependent variable. Independent variables were the concentration of bioelements. Input of independent variables was carried out by the method of forced entry. BMI and age were also introduced into the models as potential confounding factors. Regression
Coefficients are presented with 95% confidence intervals with the level of their statistical significance (p).

The critical level of significance (p) in testing statistical hypotheses was taken as 0.05.

**Research results**

On the territory of four regions - Aktobe, Mangystau, Atyrau and West Kazakhstan, children 6-12 years old were assessed for the severity of goiter endemic using modern WHO criteria. When analyzing the volume of the thyroid gland depending on the BSA and the gender of the children, we found that the 97th percentile of general thyroid volume in boys and girls in the region, regardless of their place of residence, significantly exceeds the reference values proposed by WHO. In general, in Western Kazakhstan the prevalence of thyromegaly in school-age children according to a 30-cluster analysis using the 97th percentile of the volume recommended by WHO / ICCIDD (2007) was 34.1% (95% CI:32.9-35.2), which corresponds to severe endemic. In the surveyed areas, the intensity of goiter endemic in the frequency of thyromegaly ranged from mild to severe.

The most intense endemic situation is noted in the Aktobe region - 42.7 (95% CI: 40.67-44.75)%. High prevalence of thyromegaly, corresponding to severe endemic, is observed in Aktobe - 60.7% (95% CI: 57.9-63.8), Temir - 54.8% (95% CI: 49.37-60.23 ), Mugalzhar - 43.91% (95% CI: 37.5-50.33), Alga districts - 50.0% (95% CI: 41.83-58.17). Mild endemic goiter is defined in Shalkar 7.52% (95% CI: 4.08-10.9), Khobda 12.96% (95% CI: 6.6-19.3), Uyil 15.0% (95% CI: 8.0-22.0), Kargaly 12.6% (95% CI: 8.1-17.1), Martuk 12.2% (95% CI: 7.9-16.53), Irgiz 11.49% (95% CI: 4.79-18.20), Bayganin - 14.63% (95% CI: 6.98-22.28) and Aitekebi district - 10.68% (95% CI: 4.71-17.64). Sporadic cases of thyromegaly were observed in the Khromtau region 2.88% (95% CI: 0-6.1). When comparing the prevalence of thyromegaly by gender, there is no significant difference ($\chi^2 = 0.25$ df = 1; p> 0.05): among boys, 42.2% (95% CI: 39.25-45.11), girls, 43.2% (95% CI: 40.37-46.06). When analyzing the prevalence of goiter by sex and age, starting at 9 years of age, an increase in the frequency of goiter with age is observed. The highest rates were found in 12 year old children ($\chi^2 = 21.04$ df = 1; p <0.001).

Severe goiter endemic is also observed in the Atyrau region - 33.52% (95% CI: 30.92-36.11). The highest prevalence of thyromegaly, corresponding to severe endemic, is observed in Kyzylkoga - 83.1% (95% CI: 76.93-89.26), Zhylyoi - 60.84% (95% CI: 52.84-68.84 ), Makat -53.38% (95% CI: 44.8-54.3), Inderbor districts - 44.68% (95% CI: 36.47-52.89). Thyroid endemic of moderate degree is determined in Makhambet district - 20.13% (95% CI: 13.89-26.36). Mild severity endemic in Isatai - 11.4% (95% CI: 5.57-17.24) and Kurmangazi districts - 5.71% (95% CI: 1.98-13.4). The critical situation is noted in the Kzylkoga, Zhylyoi and Makat districts, where more than 81%, 60% and 53% respectively of the population of children 6-12 years old have an enlarged thyroid gland.

When comparing the prevalence of thyromegaly by gender, the frequency of goiter does not differ ($\chi^2 = 0.87$; df = 1; p> 0.05): in boys - 34.79% (95% CI: 31.03-38.54), in girls - 32.31% (95% CI: 28.73-35.90). When analyzing the
prevalence of goiter by gender and age, its uniform distribution was revealed, but its highest level was observed among 11-year-old boys ($\chi^2 = 1.56; \text{df} = 1; p < 0.05$).

Severe goiter endemia is noted in the West Kazakhstan region - 32.5% (95% CI: 30.4-34.5). Comparative evaluation of the results of ultrasound with WHO standards revealed a number of features of the prevalence of thyromegaly in areas of the West Kazakhstan region. The highest frequencies of thyromegaly were noted in the city of Uralsk - 42.87% (95% CI: 39.62-46.12) and Akzhaik district - 42.1% (95% CI: 32.18-52.03), which corresponded to the presence of high thyroid volume. Severe goiter endemia was also found in Zelenov, Taskala and Syrym districts, where the incidence of tyromegaly was 34.21% (95% CI: 19.13-49.29), 34.65% (95% CI: 25.37-43, 93), 32.84% (95% CI: 21.59-44.08), respectively. In Kaztaloovsky, 20.4% (95% CI: 9.12-31.69), Karatobe 21.43% (95% CI: 13.83-29.03), Bukeiordinsky 22.11% (95% CI: 13, 76-30.45), Burli 22.99% (95% CI: 14.15-31.83), Terekty districts 23.81% (95% CI: 10.93-36.69) showed moderate severity goitre endemia. In other districts of the region - Chingirlau, Zhamgala, Zhanibek - the frequency of thyromegaly was 14.78% (95% CI: 8.3-21.27), 15.7% (95% CI: 8.3-21.27), 16.77% (95% CI: 10.89-22.66), which corresponded to a mild degree of goiter endemia. When comparing the prevalence of thyromegaly by gender, there is no significant difference ($\chi^2 = 2.43 \text{ df} = 1; p > 0.05$): among boys, 30.8% (95% CI: 27.9-33.7), girls 34.1 (95% CI: 31.1-37.1).

In the Mangystau region, mild endemia is determined to be 18.36% (95% CI: 15.95–20.76). The prevalence of thyromegaly in the Mangystau region was distributed as follows: in the city of Aktau - 14.62% (95% CI: 10.88-18.36), in Tuptaragan - 6.41% (95% CI: 2.57-10, 25), Munaily district - 12.75% (95% CI: 7.40-18.11) and is estimated as mild endemia. In the Karakiy district, the intensity of goitre endemia is moderate - 25.53% (95% CI: 18.33-32.73). The situation is more complicated in Mangistau and Beyneu districts, where the prevalence corresponds to 30.86% (95% CI: 20.80-40.92) and 33.59% (95% CI: 25.41-41.78) and is defined as a region with severe endemia. The prevalence of goiter among boys is 19.10% (95% CI: 15.61-22.59) and girls 17.65% (95% CI: 14.34-20.96) in the region have no statistically significant differences and exceed 5 % threshold level, determining the severity of endemia as mild. An analysis of the prevalence of thyromegaly by gender and age revealed its highest level in 11-year-old girls and boys ($\chi^2 = 1.31 \text{ df} = 1; p < 0.05$). The frequency of enlarged thyroid gland among 8-year-old children in boys is more than doubled than in girls ($\chi^2 = 4.33 \text{ df} = 1; p <0.05$).

As a result of a study of the prevalence of thyromegaly in Western Kazakhstan, against the background of sufficient iodine maintenance, severe goiter endemia was detected. Based on data from modern literature, it can be assumed that goiter endemia in the region is caused by the effect of goitrogenic factors on the body. As such, there may be a lack, an excess or an imbalance of certain bioelements responsible for maintaining the function of the thyroid gland.

In order to study the characteristics of the bioelement status of children, 498 children carried out a polyelement analysis of children's hair. The content of elements in the hair reflects the elemental status of the organism as a whole and its
biogeochemical environment. Hair samples are an integral indicator of the mineral metabolism of the human body and make it possible to assess the elemental status of a population (Skalny A.V., 2010). Given the simplicity of the method of collecting and storing hair, as well as the possibility of determining the spectrum of thyroid-specific bio-elements in the hair simultaneously with iodine, we noted a number of advantages consisting in a high concentration of elements in the hair, non-invasiveness, highly informative about the duration and nature of the elements in the body.

At the first stage of our study, we analyzed the content of bioelements, taking into account the ecological and geochemical characteristics of each region. It has been established that in terms of the bioelement composition of the hair, the examined children of Western Kazakhstan do not form a homogeneous group. The content of such elements as Al, B, Cr, Fe, Mn, P, Pb, Se, Si, Hg, Zn manifests a pronounced dependence on the place of residence, that is, is influenced by environmental and geochemical features of the environment.

Next, we carried out a comparative analysis of the content of bioelements in the hair of children relative to reference values (Skalny A.V., 2003, 2004; Iyengar V., Woittiez J., 1988). According to the results of assessing the prevalence of deviations in the content of chemical elements in the hair of the child population living in Western Kazakhstan, in all areas of WK there is a pronounced deficit of Se, Co, Cr (except for Cr deficit in Aktobe region), as well as a pronounced excess of Li, P, Si. In the Aktobe region, an excess of Cr, B, Fe, Mn, Si, P, Na, K, Li and the deficit of Se, Co, Zn are determined. Children of the Mangystau region according to hair analysis are deficient in Se, Co, Cr, Fe, I, Ni, Cu, Mn and excess of P, Zn, K, Si, Li, V. In the Atyrau region, the contents of Se, Co, Cr are lowered and contents of Li, Mn, Mg, Fe, P, Na, K, Si are risen. For children in Western Kazakhstan, there is a high frequency of deficiency of Se, Co, Cr and an excess of Li, Mn, Mg, Na, Si, P.

At the second stage of our study, we evaluated the bioelement status of children with an enlarged thyroid gland in comparison with the control and its connection with the development of thyromegaly. A comparative analysis of the content of bioelements showed an excess of the concentrations of B, Si, V in children with thyromegaly. Decreased concentrations in children with goiter were observed in such elements as Se, Co, Cr, Fe, Mn, Mg, Pb, Ni, V.

In the Aktobe region when comparing the content of bioelements in children with an enlarged thyroid gland with a group of children with normal thyroid size, we found a significant difference in the content of microelements: an increase in B content by 40.9%, and a decrease in Se by 9.3%, Co by 29, 8%, Cr by 37%, Fe by 26.7%.

In the Atyrau region, a comparative analysis of the content of bioelements in the groups with an enlarged thyroid gland and with normal thyroid size showed a significant difference: an increase in Si content by 22.6%, V by 35.1% and a decrease in Cu by 10%, Pb by 40.6 % compared with the group without thyroid.

In the West Kazakhstan region, spectral macro- and microelement analysis of the hair of children showed that the content of chemical elements in children
with thyromegaly and with the normal size of the thyroid gland (control) is significantly different. In children with goiter, there was an increase in B concentration by 32.27% and Si by 17.66%, as well as a decrease in Cd content by 37.38%, Mn by 26.48%, Pb by 47%, V by 15.5% compared with children with a normal volume of the thyroid gland.

In the Mangystau region, a comparison of the content of conditionally essential and essential trace elements showed a statistically significant difference with a decrease in rates in children with goiter. The concentration of trace elements in children with goiter increased: B by 38.5%, V by 41.5% and decreased: Se by 7.4%, Fe by 33.9%, Cr by 31.6%, Co by 41.6%, Mn by 43.2%. Ni by 37.4%, compared with children without goiter. According to the content of Si, Zn, Cu, no significant differences were found in the groups of children with goiter and without goiter. In macroelements, significant differences are associated with a decrease in Ca by 16.9% and Mg by 19.6% in children with an enlarged thyroid gland. The concentration of toxic and potentially toxic trace elements is significantly reduced in children with an enlarged thyroid gland: Al by 32.5%, Be by 37.5%, Cd by 36.9%, Pb by 49.7%, Sn by 41.5%.

Analysis of the iodine content in our study did not show any significant differences in the iodine content in the hair of children from all regions of Western Kazakhstan in the group with thyromegaly. Recent studies have shown that the iodine content in the hair is a long-term personal bioindicator of the human iodine status. In accordance with the studies of Momčilović B. et al., 2014, iodine deficiency is considered to occur when iodine concentration in the hair is less than 0.15 µg / g, at 2.0 µg / g and higher its excess is noted. In our work, we attempted to analyze the content according to the standards proposed by Momčilović B. et al. (2014) and published in the journal Thyroid. Iodine deficiency in the region is not observed, since only isolated cases of iodine deficiency are recorded according to the analysis of iodine in the hair.

Iodine metabolism directly depends not only on the amount of iodine entering the body, but is also inextricably linked to the provision of other elements that form the cofactors essential for iodine metabolism. Evaluation of the effect of other bioelements on the iodine content using the Spearman correlation analysis showed significant relationships (Tables 1-4).

Table 1 - The relationship of iodine content in the hair with the content of macro- and microelements in the hair of children 6-12 years of the Aktobe region

<table>
<thead>
<tr>
<th>Chemical element</th>
<th>Co</th>
<th>Cr</th>
<th>Fe</th>
<th>Zn</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.375</td>
<td>0.226</td>
<td>0.346</td>
<td>0.357</td>
</tr>
<tr>
<td>p</td>
<td>0.007**</td>
<td>0.028*</td>
<td>0.001**</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Note *p < 0.05; ** p < 0.01;

Table 2 - The relationship of iodine content in the hair with the content of macro- and microelements in the hair of children 6-12 years of the Atyrau region
### Table 3 - The relationship of iodine content in the hair with the content of macro- and microelements in the hair of children 6-12 years of the West Kazakhstan region

<table>
<thead>
<tr>
<th>Chemical element</th>
<th>Cu</th>
<th>Se</th>
<th>Na</th>
<th>Li</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.397</td>
<td>0.323</td>
<td>0.335</td>
<td>-0.362</td>
<td>-0.462</td>
</tr>
<tr>
<td>p</td>
<td>0.000**</td>
<td>0.001**</td>
<td>0.001**</td>
<td>0.009**</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Note *p < 0.05; ** p < 0.01;

### Table 4 - The relationship of iodine content in the hair with the content of macro- and microelements in the hair of children 6-12 years of the Mangystau region

<table>
<thead>
<tr>
<th>Chemical element</th>
<th>B</th>
<th>Cr</th>
<th>K</th>
<th>Li</th>
<th>Se</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>-0.357</td>
<td>0.330</td>
<td>0.422</td>
<td>-0.400</td>
<td>0.376</td>
</tr>
<tr>
<td>p</td>
<td>0.000**</td>
<td>0.000**</td>
<td>0.000**</td>
<td>0.000**</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Note *p < 0.05; ** p < 0.01;

Our data testified to the synergy of iodine and selenium, cobalt, zinc, iron, chromium. Antagonism of iodine and lithium, boron, lead was identified. Therefore, total hyposelenosis (98.6%), lack of cobalt (65%), excess lithium (33.5%), found in children of Western Kazakhstan can have a negative effect on iodine metabolism and thyroid hormone production. An imbalance of the elements detected in children of West Kazakhstan at the population level may contribute to the stress of the thyroid system and the formation of thyromegaly.

At the next stage of our study, we performed multiple regression analysis to prove the effect of micro- and macroelements on the volume of the thyroid gland. The volume of the thyroid gland was determined as a dependent parameter, and the factors that have a significant impact on the dependent indicator - the level of bio-elements in the hair of the children under study. Significant positive dependences of the volume of the thyroid gland on the boron content (in the Aktobe and Mangystau regions), vanadium (in the Atyrau), silicon (in the Atyrau and West Kazakhstan regions), copper (in the West Kazakhstan region). Consequently, an increase in the volume of the thyroid gland may be a consequence of an increased content in the body of these elements. In addition, a significant negative effect of iron content was found in the hair (in the Mangystau region). Accordingly, it can
be assumed that an increase in the volume of the thyroid gland is associated with a deficiency in the body of this element.

Table 5 - Results of multiple linear regression analysis of the content of microelements of hair and the volume of the thyroid gland as a dependent variable

<table>
<thead>
<tr>
<th>Predictor</th>
<th>b*</th>
<th>95% CI for b*</th>
<th>β (standart. b)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aktobe region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>-0.834</td>
<td>-1.546; -0.122</td>
<td>-0.199</td>
<td>0.022</td>
</tr>
<tr>
<td>B</td>
<td>0.290</td>
<td>0.189; 0.391</td>
<td>0.494</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Atyrau region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0.328</td>
<td>0.000; 0.656</td>
<td>0.145</td>
<td>0.040</td>
</tr>
<tr>
<td>Si</td>
<td>0.027</td>
<td>0.008; 0.046</td>
<td>0.209</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>West Kazakhstan region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu</td>
<td>0.203</td>
<td>0.134; 0.272</td>
<td>0.410</td>
<td>0.000</td>
</tr>
<tr>
<td>V</td>
<td>-11.727</td>
<td>-19.576; -3.879</td>
<td>-0.206</td>
<td>0.004</td>
</tr>
<tr>
<td>Si</td>
<td>0.024</td>
<td>0.002; 0.046</td>
<td>0.151</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>Mangystau region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.104</td>
<td>0.020; 0.188</td>
<td>0.193</td>
<td>0.016</td>
</tr>
<tr>
<td>Fe</td>
<td>-0.022</td>
<td>-0.046; 0.002</td>
<td>-0.183</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Note* - * corrected regression coefficients with 95% confidence intervals were calculated and corrected for BMI and age.

A comparative analysis of the content of bioelements in the groups with an enlarged and normal thyroid gland also showed excess concentrations of B (by 40.9% in Aktobe, by 38.5% in Mangystau, 32.3% in WK, by 22.6% in Atyrau), Si (by 17.7% in WK, by 41.5% in Mangystau, by 35.1% in Atyrau) in children with thyromegaly.

Thus, our study showed a high prevalence of thyromegaly in children of Western Kazakhstan. Analysis of the bioelement status showed that an increase in the volume of the thyroid gland may be the result of an imbalance of microelements, which was promoted by the current unfavorable ecological situation in the region. The increased concentration of chemical pollutants in the environment can lead to a violation of bioelement metabolism, and further, the formation of goiters.

After analyzing the relationship of the content of bio-elements in the hair with the volume of the thyroid gland, we can ascertain the significant effect of boron (in the Aktobe and Mangystau regions), vanadium (in the Atyrau and West Kazakhstan regions), silicon (in Atyrau and West Kazakhstan regions), chromium (in the Aktobe region), copper (in the West Kazakhstan region) and iron (in the Mangystau region) in the formation of thyromegaly.

Considering the fact that at the present time, along with biogeochemical endemics of natural origin, endemic diseases that are a reaction to the abnormal composition of the natural environment, altered man-made human activity (Veldanova M.V., 2002) are widespread, we concluded that the high prevalence of thyromegaly in The region may have an anthropobiogeochemical nature, and
thyroidal should be considered as a manifestation of a pronounced imbalance of bioelements, due to the natural and technological influence of the environment.

According to the study, it should be noted about the need for an integrated approach to protecting the health of children in the region with a high environmental load. The results we obtained indicate the need for measures to prevent and early diagnose disorders of the bioelemental balance in children of West Kazakhstan. In order to prevent the development of thyromegaly in children in the region, it is necessary to carry out timely diagnosis of imbalance of bioelements and to take into account the identified changes in elemental homeostasis in the program of corrective measures. According to the results of the study, we proposed an algorithm for diagnosing and correcting the imbalance of the thyroid-specific elements - selenium and cobalt in children with an enlarged thyroid gland. The scientifically grounded developed algorithm presented by us will allow early diagnosis of the children of the region, effective correction of the strumogenic effect of low selenium and cobalt contents.

The results of the study and their analysis allow us to draw the following conclusions:

1. The prevalence of thyromegaly in school-aged children in the region, according to WHO criteria, was 34.1% (95% CI: 32.9-35.2), which corresponds to severe endemia. In the surveyed areas, the intensity of goiter endemia in the frequency of thyromegaly ranged from mild to severe. The most intense endemic situation is observed in the Aktobe region - 42.7 (95% CI: 40.67-44.75) %, in the Atyrau region - 33.52% (95% CI: 30.92-36.11) and the West Kazakhstan region - 32.5% (95% CI: 30.4-34.5). In the Mangystau region mild endemia is determined to be 18.36% (95% CI: 15.95–20.76).

2. A common indicator of the imbalance of the elemental profile of children living in Western Kazakhstan is a deficiency of selenium and cobalt, an excess of silicon and lithium. A distinctive feature of the elemental status of the examined children in the Aktobe region was an excess of chromium, boron, iron, manganese and zinc deficiency, in the Mangystau region - an excess of boron, zinc and deficiency of chromium, iron, iodine, nickel, copper, manganese, in the Atyrau region - an excess of manganese, magnesium, iron and chromium deficiency and in the West Kazakhstan region - chromium deficiency with an excess of manganese, magnesium.

3. Imbalance of bioelements is manifested by population deficiency of selenium (in 98.6% of children), cobalt (in 65% of children), excess lithium (in 33.5% of children), and silicon (in 30% of children). The increase in the volume of the thyroid gland in Western Kazakhstan is due to the significant influence of boron ($\beta = 0.494, p = 0.00$ in the Aktobe region; $\beta = 0.193, p = 0.016$ in the Mangystau region), vanadium ($\beta = 0.145, p = 0.04$ in the Atyrau region; $\beta = -0.206, p = 0.004$ in the WKR), silicon ($\beta = 0.209, p = 0.01$ in the Atyrau region; $\beta = 0.151, p = 0.033$ in the WKR).
PRACTICAL RECOMMENDATIONS

In the process of monitoring the state of goiter endemic in the region in order to identify strumogenic factors, it is necessary to assess the bioelemental status of children 6-12 years of age.

General practitioners, pediatricians, endocrinologists, due to the presence of severe goiter endemic in the region in the detection of thyroid pathology, along with the use of a wide range of laboratory tools, should carry out an assessment of the bioelemental status. If an imbalance of bioelements is detected, they should carry out comprehensive measures for group and individual correction of deviations in the bioelement status against the backdrop of mass prevention of iodine deficiency. It is recommended to eliminate the identified population deficiency of essential elements (selenium and cobalt).

Regional health authorities are recommended to develop regional measures for the prevention of goiter endemic caused by the strumogenic effect of imbalance of bioelements by correcting deviations in bioelement status with adequate nutritional deficiencies of micro- and macronutrients (enrichment of food rations with products with a high content of missing elements, use of therapeutic and preventive products).

In order to timely diagnose and prevent the development of thyromegaly in children in the region, it is advisable to use the algorithm for diagnosing and correcting Se, Co hypoelementoses.