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**ORIGINAL PAPER**

# HAIR TRACE ELEMENT COMPOSITION IN 6- TO 12-YEAR-OLD CHILDREN WITH GOITER IN WEST KAZAKHSTAN, A PROVINCE OF THE REPUBLIC OF KAZAKHSTAN*

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## Abstract

The western part of the Republic of Kazakhstan is where gas and oil are mined, which causes numerous ecological problems due to environmental pollution. Meanwhile, high prevalence of goiter is observed in the region. This study aimed at identifying levels of trace elements in hair of children with goiter living in West Kazakhstan. The research included 159 school children, 6 to 12 years of age, with the body mass index of 14 up to 20 kg $m^{-2}$. Thyroid ultrasonography was used to measure the thyroid volume and the ellipsoid model was used for calculations. Trace elements were determined by ICP-MS (inductively coupled plasma mass spectrometry) using a spectrometer NexION 300D (Perkin Elmer Inc., USA). The study demonstrated that the iodine content in the hair of children corresponded to an adequate iodine status, but excess values for boron (up to 32.29%) and silicon (21.44%) were identified in children with goiter as compared with the control group. A decrease in the indicators for cadmium (down by 37.38%), manganese (26.48%), lead (47%) and vanadium (15.5%) was observed in comparison to children with normal volume of the thyroid gland. Results of the multiple regression analysis revealed that the volume of the thyroid gland_was positively correlated to the concentrations of copper and silicon in hair and negatively, although less strongly, correlated to the vanadium concentration. Thus, children with goiter had higher levels of boron and silicon in hair as well as reduced levels of cadmium, manganese, lead and vanadium. Thyroid volume was positively correlated to the concentration of copper and silicon in the hair but negatively, although less strongly, correlated to the hair vanadium content.

**Keywords:** goiter, children, Kazakhstan, silicon, copper, vanadium, manganese, Ural River.

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# INTRODUCTION

Despite mass-scale iodine prophylaxis, endemic goiter remains an urgent medical and social problem due to its wide prevalence in people of any age. In recent decades, much progress has been reached worldwide in eliminating iodine deficiency disorders. The number of countries in the whole world with iodine deficiency has decreased from 54 to 30, while the number of those with sufficient iodine intake has increased from 67 to 112 (Zimmermann 2013). Nevertheless, according to the WHO (World Health Organization) estimates, thirty countries in the world are still experiencing iodine deficiency, 29.8% of school-age children have insufficient iodine intake, and only 70% of households have access to iodized salt (Zimmermann, Andersson 2012). The state policy to prevent iodine deficiency is carried out in the Republic of Kazakhstan, and in 2010 the country was ascertained to eliminate iodine deficiency through universal salt iodization.

However, a steady growth of the thyroid gland in children and adults is observed in the western part of the Republic of Kazakhstan. An assessment of the severity of iodine deficiency in accordance with the WHO criteria shows that West Kazakhstan can be classified as a region with a severe degree of endemic goiter prevalence (Kudabaeva et al. 2015).

Iodine deficiency is the leading causal factor in the development of goiter. Besides, other causes which aggravate the negative impact of iodine deficiency may contribute to the formation of endemic goiter. Combined effects of goitrogens of various origin are probable, including natural iodine deficiency, substances of technogenic origin, trace element imbalance (Pearce, Braverman 2009, Duntas 2015).

Various other trace elements apart from iodine can affect the thyroid function. Selenium deficiency contributes to the prevalence of thyroid disease (Wu 2015). Thyroid metabolism is affected by silicon, cobalt, magnesium (Gorbachev et al. 2007), copper, cadmium, lead and chromium (Rana 2014). The development of goiter is caused by accumulation of toxic metals – lead, cadmium and manganese (Savchenko, Toupeleev 2012). Therefore, to understand the reasons for the high prevalence of goiter in the region it is necessary to study the possible role of microelements in goiter development.

This study aimed to trace concentrations of aluminum (Al), boron (B), copper (Cu), selenium (Se), manganese (Mn), cadmium (Cd), lead (Pb), silicon (Si) and vanadium (V) in hair of children with goiter living in West Kazakhstan.

## MATERIAL AND METHODS

A cross-sectional study was conducted on the territory of West Kazakhstan (the Republic of Kazakhstan). The study of the goiter prevalence in the region was carried out in accordance with the principles of the Helsinki Declaration and subsequent amendments. The study was approved by the Local Ethics Committee (Protocol № 06/01-7, 05.01.2013). Informed consent for examination was obtained from the parents or legal representatives of children.

The following exclusion criteria were used in this study:

(I) acute infections, surgical and traumatic diseases;

(II) endocrine diseases;

(III) metal implants (including dental amalgam);

(IV) vegetarian meals;

(V) consumption of vitamin and mineral supplements.

Biomonitoring of hair microelement composition was performed in 159 children aged 6 to 12 years, living constantly in this residential area. The body mass index (BMI) of children was within the range of 14 - 20 kg $m^{-2}$.

The study was conducted in accordance with the WHO recommendations, due to the subjects' high exposure and vulnerability to iodine deficiency and availability for study (WHO 2007). The study included 75 boys and 84 girls, whose average age was 9.3 ± 0.9 years.

An Aloka SSD-500 (Aloka, Tokyo, Japan) apparatus with a 7.5-MHz linear transducer was used to perform ultrasonography of the thyroid. Ultrasound was also used to measure the thyroid volume, with the ellipsoid model (width x length x thickness x 0.52 for each lobe) being used for calculation. Samples of hair (0.1 g) were taken from the occipital area using pre-treated stainless steel scissors. Samples were washed with acetone and rinsed thrice with deionized water with subsequent air drying at 60°C. The samples were digested with concentrated $HNO_3$ at 180°C for 20 min in a Berghof Speedwave 4 system (Berghof Products & Instruments, Germany). The analysis of trace elements (Al, B, Cu, Se, Mn, Cd, Pb, Si, V) in the samples was carried out at the Center for Biotic Medicine (Moscow), applying ICP-MS (mass spectrometry with inductively coupled plasma) on a spectrometer NexION 300D (Perkin Elmer Inc., USA) equipped with a sampler ESI SC-2 DX4 (Elemental Scientific Inc., USA). System calibration was performed using a set of standards of Universal Data Acquisition Standards Kit (Perkin Elmer Inc., USA). Internal standardization was performed online with a solution of Yttrium-89 isotope produced from Yttrium (Y) Pure Single-Element Standard (Perkin Elmer Inc., USA). A certified standard sample of human hair GBW09101 «Humanhair», issued by the Shanghai Institute of Nuclear Research (China) served as the standard sample.

To examine the relationship between the trace element status and the volume of thyroid gland, the children were allocated into 2 groups: children with goiter ($n$ = 70, girls / boys – 36% / 64%) and children without goiter ($n$ = 89, girls / boys – 61% / 39%).

**Statistical analysis**

The data were processed using software Statistica.10 (StatSoft Inc., USA). Distribution of data was assessed using the Shapiro-Wilk test. Data distribution on trace elemental composition was different from the normal hair indicators. In this regard, median and interquartile range -25 and -75 percentile (median (25-75)) were used for the descriptive statistics. Group comparisons were performed with the Mann-Whitney $U$ test. Correlation analysis was performed on the basis of the Spearman's rank correlation coefficient. The level of significance was set as $P < 0.05$ for all analyses. Variables correlated with the volume of the thyroid gland at $P < 0.05$ were included in the multiple linear regression model.

# RESULTS AND DISCUSSION

Data of anthropometric characteristics showed no significant differences in BMI values between the group of children with goiter and the control group (Table 1). Spectral analysis of the hair trace elements in children with goiter

Table 1

Characteristics of the surveyed children aged 6 to 12 years, West Kazakhstan province

| Anthropometric characteristics | Children with goiter ($n$ = 70) | Children without goiter ($n$ = 89) | $P$-value |
|---|---|---|---|
| Height (cm) | 131.4 ± 6.49 | 134.7 ± 6.44 | 0.002 |
| Weight (kg) | 27.51 ± 4.32 | 29.52 ± 4.56 | 0.005 |
| BMI (kg $m^{-2}$) | 15.84 ± 1.33 | 16.19 ± 1.53 | 0.134 |
| BSA ($m^2$) | 1.02 ± 0.09 | 1.07 ± 0.11 | 0.003 |
| Thyroid gland volume (ml) | 5.79 ± 2.51 | 3.21 ± 0.81 | 0.000 |

and with a normal size of the thyroid gland (control group) revealed that the content of B, Mn, Cd, Pb, Si, V was significantly different (Table 2). Increased accumulation of B and Si was marked in hair samples from children with goiter, while the content of Cd, Mn, Pb, V was reduced in this group.

Correlation analysis showed a significant positive relationship between the volume of the thyroid gland and the content of trace elements in hair for Cu ($r$ = 0.423; $P$ = 0.001) and Si ($r$ = 0.202; $P$ = 0.01). Other trace elements showed a minor negative correlation with the size of the thyroid gland: Al ($r$ = -0.182; $P$ = 0.022), Se ($r$ = -0.166; $P$ = 0.037). Results of the analyses are presented in Table 3.

Table 2

The content of trace elements in the hair of children aged 6 to 12 years, West Kazakhstan province (μg $g^{-1}$)

| Chemical element | Children with goiter (*n* = 70) | | Children without goiter (*n* = 89) | | *P*-value |
|---|---|---|---|---|---|
| | Me | q25–q75 | Me | q25–q75 | |
| Al | 9.306 | 6.038-12.60 | 12.64 | 6.01-17.72 | 0.091 |
| B | 1.975 | 1.070-2.526 | 1.337 | 0.774-1.820 | 0.002* |
| Cu | 9.076 | 8.278- 10.18 | 9.028 | 8.136-10.43 | 0.801 |
| Se | 0.434 | 0.385-0.480 | 0.450 | 0.414-0.507 | 0.053 |
| Mn | 0.921 | 0.502-1.475 | 1.252 | 0.660-2.047 | 0.034* |
| Cd | 0.038 | 0.017-0.071 | 0.061 | 0.031-0.135 | 0.002* |
| Pb | 0.681 | 0.370-1.359 | 1.285 | 0.619-2.455 | 0.002* |
| Si | 23.74 | 15.74-31.87 | 19.55 | 14.68-25.34 | 0.023* |
| V | 0.045 | 0.029-0.068 | 0.053 | 0.036-0.085 | 0.043* |

* significant difference

Table 3

Relationships between total thyroid volume with the content of trace elements in the hair of children aged 6 to 12 years

| Criteria | Al | Cu | Se | Si |
|---|---|---|---|---|
| *r* | -0.182 | 0.423 | -0.166 | 0.203 |
| P | 0.022 | 0.000 | 0.037 | 0.010 |

*r* – correlation coefficient, *P* – individual *p* values for the interaction

Data of the multiple regression analysis (Table 4) showed that Cu and Si may positively influence the volume of the thyroid gland, and V may have a negative effect. The analysis led to an equation of the regression presenting the dependence of the total volume of the thyroid and the Cu, Si and V concentration in hair:

$$Y = 2.461 + 0.410\ Cu + 0.151\ Si - 0.206\ V,$$

where Y – thyroid gland volume.

Table 4

Multiple linear regression analysis of the content of trace elements in hair and thyroid gland volume as a dependent variable

| Element | *β* | t (155) | *P*-value |
|---|---|---|---|
| Cu | 0.410 | 5.837 | 0.000 |
| V | -0.206 | -2.952 | 0.004 |
| Si | 0.151 | 2.153 | 0.033 |

F(3.155) = 16.82 $P^* < 0.000$, $R^2 = 0.246$; adjusted $R^2 = 0.231$
*P* – individual *P* value; *P** – *P* value for the model

In Kazakhstan, endemic goiter has been reported in 11 out of 14 regions, and a shortage of iodine in the soil, water and food was determined in half of the country's territory (UNICEF 2005). Therefore, in accordance with the national regulations, almost all salt produced in Kazakhstan, as well as imported into the Republic, is enriched with iodine (*Law…* 2003). After 8 years of universal salt iodization in the Republic of Kazakhstan, studies convincingly proved that the problem of iodine deficiency in the Republic had disappeared (Ospanova et al. 2013). According to data of the Iodine Global Network (2015), currently, the iodine status of the population in Kazakhstan corresponds to more than an adequate level. Besides, 85.4% of households have access to iodized salt.

However, despite the absence of iodine deficiency in the Republic, high prevalence of goiter in Western Kazakhstan is observed (Kudabayeva et al. 2014). Kazakhstan has significant reserves of oil and gas, which are mined in the western part of the Republic of Kazakhstan. It is known that the mining and processing of these resources cause many environmental problems due to pollution by oil products, heavy metals, carbon, sulfur, nitrogen oxides and other substances (Dahl, Kuralbayeva 2001, Kaiser, Pulsipher 2007).

According to the results of the multiple regression analysis, we found that the content of copper in hair had a positive effect on the volume of the thyroid gland and a reliable significant correlation between the two factors was detected. In fact, copper is a part of the cytochrome oxidase enzyme necessary for the oxidation of iodine inside of thyrocytes and ATP formation is involved in the synthesis of thyroid hormones. In a study based on data from a regression analysis, it was determined that tcopper levels were associated with increased levels of thyroid hormones (Jain 2014). In the study Kazi et al. (2010) significantly higher levels of the copper content and the lower values of iron and iodine were observed in serum and urine samples of patients with goiter than in the control group.

West Kazakhstan lies in the western part of the Republic of Kazakhstan and occupies an area of 151.3 thousand sq. km. Almost half of the province's population live in the Ural River valley, which flows from Bashkortostan, then crosses the territory of the Chelyabinsk and Orenburg provinces in Russia, next flows through West Kazakhstan and Atyrau in Kazakhstan, where settlements with a total population of 4.5 million people are situated along the river banks, and the length of the Ural River within West Kazakhstan is 761 km. Major industries are located along the course of the Ural River and its tributaries, including such facilities as the Karashyganak Oil and Gas field, Orenburg Gas processing complex, metallurgical plants for mining and processing of copper and chromium (Sivokhip, Chibilev 2014).

According to the State's report "On the State and Environmental Protection of the Orenburg Region in 2014", the degree of pollution of the Ural River and its left tributary, the Ilek river, was identified as "very polluted" and "dirty". The content of toxic elements exceeds several times the maximum permissible concentration (MPC). Average annual concentrations of major pollutants in the sampling sites on the Ilek river (village Vesely) and the Ural River (village Ilek) reached 6.5 and 3.6 MPC for copper, 1.4 and 1.2 MPC for petroleum products, 4.8 and 1.7 MPC for nitrite nitrogen, 2.3 MPC for ammonia nitrogen, 1.1 MPC for easily oxidized organic substances by $BOD_5$ (biochemical oxygen demand), 1.8 MPC for organic matters COD (chemical oxygen demand). The maximum concentration of organochlorine pesticides reached 0.3 MPC. Literature data describe the effect of water sources along a river on thyroid pathology. It was found that the sources of drinking water from the lower course of the Yangtze River were causing disruption of thyroid hormones. The chemicals destroying thyroid hormones, such as organochlorine pesticides and phthalate esters, were found in water sources. In addition, tests showed that the water from the Yangtze River, Yellow River, Taihu Lake and the ground water in the Yangtze River Delta region have an antagonistic effect on thyroid receptors (Hu et al. 2012, Shi et al. 2012). These studies show that living in a river valley and the level of contamination can have a negative impact on thyroid function.

Our data show the effect of the excess of silicon causing an increase in thyroid volume. This result is consistent with the study into the microelement status in children living in a territory with adequate iodine levels (Gorbachev et al. 2007). In our study, we found a weak positive correlation between the silicon concentration in hair and the total thyroid volume. The effect of silicon on the function of the thyroid gland has been studied in experiments on rats. An increase in the level of thyrotropin was observed, whereas the concentrations of triiodothyronine and thyroxine were not changed (Najda et al. 1993). Vanadium plays an important physiological role in the metabolism of iodine and the function of the thyroid gland. In an experimental study on rats it was proven that vanadium deprivation effected an increase in the weight of the thyroid gland (Uthus, Nielsen 1990). In experiments on rats by intraperitoneal injection of aluminum it was found that aluminum does not disturb the function of the thyroid gland, however can indirectly affect thyroid iodide uptake and hormones secretion by the induction of an oxidative stress state (Orihuela 2011).

In our previous study we found an excessive amount of boron in hair of children living in areas of oil and gas mining in the Aktobe province (Kazakhstan), also the effect of boron on the volume of the thyroid gland has been proven in a statistical model (Kudabayeva et al. 2016). The study of water in the Ilek River testified to the ecological status of the cities of Aktobe and Alga as being “a disaster zone” and “an emergency zone”, respectively. An analysis of water and sediment in the Ilek River proved that major pollutants were boron and chromium (Berdesheva et al. 2014). There is evidence that addition of boron reduces the hormone triiodothyronine in the serum of experimental animals (Armstrong et al. 2001). In other studies, analysis of the boron content in serum was not associated with the thyroid markers (Harari et al. 2015).

Undoubtedly, selenium deficiency plays an important role in the development of goiter, by accompanying iodine deficiency, particularly in goiter endemic areas (Çelik et al. 2014). The role in the development of thyroid pathology is explained by the fact that selenium in the content of deiodinase peripherally converses thyroxine into triiodothyronine (Żarczyńska et al. 2013, Schweizer, Steegborn 2015). According to the research accomplished in Turkey, lower levels of selenium in the blood serum were found in children with goiter than in children without this health probmen, thus confirming the fact that selenium deficiency plays an important role in the goiter development (Cinaz et al. 2004). Changes in the concentration of metabolites in the group with selenium deficiency, induced by compensatory regulatory mechanisms, compared with the control, were observed in the experiments on mice (Mickiewicz et al. 2014). However, according to the cross-sectional study of a Chinese population in an iodine-sufficient area, the content of selenium in the blood serum was not related to the volume of the thyroid gland and no difference in the content of selenium in the groups with and without goiter was found (Liu et al. 2013).

We found no differences in the levels of selenium between groups with and without goiters, despite the proven role of the selenium deficiency in the development of goiter. Although in comparison to Moroccan children (El-Fadeli et al. 2016.) we found out that Kazakh children demonstrated a lower level of selenium, which was approximately half of that determined in children in Morocco. This interesting finding is connected with differences in the nutrition of Moroccan and Kazakh children.

In our study, reduced levels of manganese, cadmium, lead, vanadium were found in the hair of children with goiter. The study of Błazewicz et al. (2010) proved that the concentrations of copper, manganese, iron and zinc in the thyroid gland were significantly lower in patients with thyroid nodules than in healthy people. It has been shown that there was a positive link between cadmium exposure and the concentration of thyroid hormone in adults, indicating that cadmium increases the level of thyroid hormones (Chen et al. 2013).

Lowered manganese indicators were observed in the study of Memon et al. (2015). When comparing the level of manganese in serum of female patients with hypothyroidism, hyperthyroidism and in the reference group, a significant reduction of manganese was found in patients having hypothyroid disorder. Manganese deficiency is one of the factors of goiter development, which is likely related to its participation in thyroid hormone synthesis because of the presence in Mn superoxide dismutase. More than 20 elements affect the normal physiology of the thyroid (Zaichick et al. 1995). Even a small shift in the balance of trace elements can change the function of the thyroid gland.

# CONCLUSIONS

An increase in the volume of the thyroid gland may be the result of some imbalance of microelements, which is promoted by the unfavorable ecological situation in the western part of the Republic of Kazakhstan. In children with goiter, the lack of balance between trace elements seems to be associated with an increase in the content of boron and silicon and a decrease in the level of cadmium, manganese, lead and vanadium in hair, as was observed in our study.

## Competing interests

All authors declare that they have no competing interests.

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