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Detection of Iodine Deficiency Disorders (Goiter and Hypothyroidism) in School-Children Living in Endemic Mountainous Regions, After the Implementation of Universal Salt Iodization

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Physiological aspects

Iodine and thyroid hormones are indispensable for somatic growth and development of several organs and systems in the fetus and infant. Their most important action is on the development of central nervous system in the critical period of life: from the fetal life up to the third year of age (Dobbing & Sands, 1973; Delong, 1989; Delange, 2000; Koibuchi & Chin, 2000). Thyroid hormone primary is involved in myelination and neuronal-glial cell differentiation (Bernal, 2005), brain maturation, and is crucial in the development and maintenance of normal physiological processes (Joffe & Sokolov, 1994, Neale et al., 2007).

1.2. Etiology and pathophysiology of Iodine Deficiency Disorders (IDD)

Insufficient dietary iodine intake is the most important etiological factor of disorders caused by iodine deficiency, but goitrogens (perchlorates, thiocyanates), physiological periods with high requirement of iodine (puberty, pregnancy, lactating period), increased urinary iodine excretion (nephrosis syndrome), high thyroxine binding globuline level (hyperestrogenism, oral contraceptives), lack of selenium, latent thyroid enzyme defects and autoimmune thyroid processes may contribute as well (Brook et al., 2008; Delange & Dunn, 2005).

Insufficient iodine intake leads to reduced thyroid hormone production, and all the consequences of iodine deficiency.

Iodine deficiency occurring during the critical period of life induces the most damaging complications: irreversible mental retardation and cretinism (Hetzel, 1983; Stanbury, 1994; Delange, 2001; Boyages, 1994; Bleichrodt, 1994). In severely endemic areas, cretinism may affect up to 5-15% of the population, being the most common cause of mental retardation (Glinioer, 2001, Morreale de Escobar et al., 2004; Pearce, 2009). However, milder brain impairments appear most frequently, such as poor school performance, reduced intellectual ability, impaired work capacity (Stanbury, 1994), apathy, lassitude, diminished mental capacity, verbal and hearing impairments.

In children iodine deficiency causes goiter and reduced growth velocity as well. During time diffuse goiters can transform into uni- or multinodular goiters. These nodules can become autonomous, inducing hyperthyroidism, especially after administration of iodine.

1.3. Clinical aspects – High-risk populational groups

Iodine deficiency induces a large spectrum of organic and functional consequences grouped under the general heading of iodine deficiency disorders (IDD) (Hetzel, 1983). IDD reflect this public health problem more relevantly than the term „goiter“. This group of disturbances is characterised by all of the ill-effects of iodine deficiency specific to different physiological stages (fetus, newborn, infant, schoolchild, adolescent, adult, especially pregnant woman) (Hetzel, 1983; Stanbury, et al., 1998; Lauberg et al., 2000; de Benoist et al., 2004; Delange & Dunn, 2005), that can be prevented by adequate intake of iodine.

The population groups being at the highest risk to develop IDD and severe consequences are fetuses, children under 2 years of age, pregnant and lactating women. The most devastating outcome of IDD is increased perinatal mortality and mental retardation. In infants iodine deficiency is the most frequent cause of preventable mental damage worldwide (de Benoist et al., 2004).

In school-age children and adolescents the main clinical manifestations are diffuse endemic goiter, subclinical thyroid dysfunctions (mainly hypothyroidism and rarely hyperthyroidism), and impaired mental function, retarded physical development as the impact of iodine deficiency on the central nervous system. The iodine-deficient thyroid gland in children is highly susceptible to nuclear radiation (Hetzel, 1983; Stanbury et al., 1998; Lauberg et al., 2000; de Benoist et al., 2004; Delange & Dunn, 2005; Zimmermann, 2009; Andersson et al., 2007).

In moderate iodine-deficient regions hypothyroidism may appear in children (Brook et al., 2008), at the same time delayed neurodevelopment with defective neuromotor and cognitive ability were also met (Vermiglio et al., 1990; Bleichrodt & Born, 1994; Pop et al., 2003).

Clinically euthyroid school-children in iodine-deficient regions have subtle or overt neuropsychointellectual deficits compared to iodine-sufficient children in the same ethnic, demographic, nutritional and socioeconomic system (Vermiglio et al., 1990; Fenzi et al., 1990). The

intelligence quotient may be reduced with about 10-15% in children living in mild, moderate iodine deficient areas (Bleichrodt & Born, 1994).

The attention deficit and hyperactivity disorders (AD-HD) appear significantly more frequently in mild-moderate iodine-deficient geographical areas than in iodine-replete regions (Vermiglio et al., 2004). AD-HD was often observed in developed European countries known currently with mild-moderate iodine deficiency (Vermiglio et al., 2004).

1.4. Epidemiology

Several regions worldwide are believed to be iodine deficient of different degree, but the true extent is not fully known. 50% of the world population was estimated to live in countries with iodine deficiency. IDD represented a major public health problem in the whole world at the end of the 20th and the beginning of the 21th century. In 1999 IDD did affect 2.225 billion people (38.4% of the world population) in 130 countries. About 700 million people (12.6% of the population) had goiter (WHO et al., 1999). In 1994, 43 million individuals were estimated to be mentally handicapped as a consequence of iodine deficiency.

Europe is considered a mild to moderate iodine-deficient continent. Endemic goiter was often reported in Europe, especially in mountainous areas. The reevaluation of iodine status in the late 1980's indicated that most European countries were still iodine deficient (Gutekunst & Scriba, 1989). Thus, programs for the elimination of iodine deficiency were initiated in several regions. In 1997 a study involving 26 European countries showed mild to severe iodine deficiency in many regions, and a dramatic return of the deficiency within 5 to 7 years after the interruption of iodized salt program (Delange et al., 1998). In 1999 the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) reported that 18 countries in Western and Central Europe, including Romania and 14 countries in Eastern Europe were still affected by iodine deficiency; then Denmark, France and Ireland were added to them. About 275 million people (31.6% of the population) were affected by IDD, and 130 million had goiter (15%) (WHO et al., 1999).

Romania was considered an European endemic region at the end of the 20th century, where goiter frequency was very variable in different areas. The highest frequency was reported in hilly-mountainous regions, such as Maramureş (mountainous northern zone) the Carpathian Mountains, as well as the Transylvanian Basin (located at the center of the country). In 1993 the incidence of goiter was 1.19-26.45% in school-age children. In 1994-1995 the Thyromobil project realized in Braşov and Timişoara districts detected goiter by ultrasound in 13.5% of boys and in 10.1% of girls with age between 6-12 years. The incidence of goiter assessed by physical examination was 2.9-36.3% in 16 counties (Simescu & Ionescu, 1998). In conclusion, at the end of the 20th century iodine deficiency disorders remained a serious public health problem in our country.

During 2002-2004 the evaluation of iodine status in the whole territory of Romania has shown that 80% of the counties (especially rural regions) were moderately iodine deficient areas, the prevalence of endemic goiter was 0-40% and urinary iodine excretion

(UIE) was reduced in 2/3 of studied individuals, detecting very low levels in pregnant women (Goldner, 2005).

Mureș County is a 6,700 square km large hilly-mountainous region in Transylvanian Basin, located in the center of Romania, populated with about 600,000 inhabitants. Similar investigations were performed here in 1950's (Cornea, 1957), which were continued until the '80 years, some of the results being published (Vasilescu et al., 1986, Hetzel et al., 1987). After that IDD survey by modern methods (UIE and thyroid ultrasound volumetry) were recommended. In 1998-1999 school-children from localities near the superior and middle hydrographical basin of the river Mureș, including Târgu Mureș (the capital city of Mureș County) were screened. The results showed mild iodine deficiency in most rural localities, moderate iodine deficiency in some villages, and normal iodine state in Târgu Mureș (Balázs et al., 1998, 2000/a, 2000/b). Our survey targeting neonatal and maternal screening, performed during 2001-2006, investigated the impact of universal salt iodization on the iodine status of these high-risk populations, and it showed that Mureș County is a moderately mild iodine-deficient area (Kun et al., 2003, Kun, 2006, Kun et al., 2007, Szántó et al., 2007).

1.5. Official strategies to eliminate iodine deficiency disorders worldwide

In 1990 the heads of States and Governments and other senior officials on the occasion of the World Summit for Children assumed a solemn obligation to eliminate the iodine deficiency disorders. In 2002 an international agreement for the long-term elimination of IDD until 2005 was accepted at the special Session of UNO dedicated to childhood health. The World Health Organization criteria to eliminate IDD through universal iodization of alimentary salt were the use of iodized salt at least in 90% of households, adequate iodine-concentration of salt (20-40mg/kg), and the implementation in practice of these measurements at least within two years. Reviewing the IDD status in Europe, a marked improvement in the status of iodine nutrition was observed, especially in the central parts of the continent (Delange, 2002; Vitti et al., 2003, Gerasimov, 2002).

1.6. National strategy on the elimination of IDD in Romania

The legislative measures for the elimination of endemic goiter were controlled for decades by the 637/1955 and the 1056/1962 Governmental Decisions, which ordered among others the distribution of potassium iodide (KI) tablets in school-age children. Thus, legislation on salt iodization did exist, but being not enforced it could not eradicate goiter. So, several Romanian counties, especially hilly-mountainous and rural regions remained iodine deficient according to the above presented data. In 1995 a new governmental order (No. 779/1995) proposed to review the prevention measures of IDD. In 1997 the 21 National Program of the Romanian Ministry of Health intentioned to reduce the frequency of IDD with at least 10% during the following 5 years. Romania has been taken part at the European strategy to eliminate iodine deficiency in Europe on the basis of the WHO criteria from 2002. Extended surveys were performed in Brașov County, Banat (in the central and the western region of the country, respectively, both being parts of the Thyromobil project), Moldova (the eastern ter-

ritory) and Dobrogea (south-eastern region), as well as Bucharest, the capital of the country (Simescu, 1999). The nationwide surveys conducted in 2002 have shown that non-iodized salt was still present in Romanian households: 31% of the households in urban and 37% in rural localities (Government of Romania, 2005).

In the frame of the general strategy the following measurements were taken: a governmental decision (No. 586/5 June 2002) was adopted regarding universal salt iodization (mean KIO_3 content of salt $34 \pm 8.5 \text{ mg/kg}$ – i.e. 25.5–42.5 mg/kg, higher than previously); the use of iodized alimentary salt has become mandatory since 2003, and the compulsory iodization of salt used in baking industry was decided in 2004. In addition, the National Committee for universal salt iodization and IDD elimination (with multisectorial participation) was founded in 2004; in the same year the National Strategy on the elimination of IDD during 2004–2012 was elaborated and adopted by governmental decision (Government of Romania, 2005). In 2005 the National Strategy on the elimination of IDD was founded in the Institute of Public Health București. Consequently, the use of iodized salt in households increased to 96% in 2004 (compared to 53% in 2002) according to data furnished by the Institute of Mother and Child's Protection, but on the other hand iodine content of alimentary salt proved to be insufficient (63%). Therefore, iodine supplementation was necessary, and 10% of school-children received iodine tablets, prescribed by general practitioners. Consequently the iodine-supplementation of school-children and pregnant women has improved considerably after the first 2 years of obligatory use of iodized alimentary salt, the urinary iodine excretion (UIE) becoming almost normal. With all the efforts IDD was still persisting in 2005, requiring enforced monitoring system of iodized salt production and consumption, strengthen the health promotion network etc. (Goldner, 2005).

1.7. Indicators to assess baseline IDD status and to monitor and evaluate the IDD control programs

Individual evaluation of IDD is based on clinical exam (physical examination to determine thyroid size and signs of thyroid dysfunctions, inclusion the case into populational group at risk for IDD, psychoneurosomatic assessment of children and adolescents), as well as laboratory and imagistical findings (UIE, TSH, FT_4 , FT_3 , radioiodine uptake, thyroid ultrasound and scintigraphy, fine-needle aspiration biopsy of thyroid nodules).

The epidemiological evaluation of a geoclimatic area includes the determination of iodine content of the water and soil, and the assessment of different types of IDD in the population by indicators of iodine status at baseline and during the salt iodization program (impact indicators: median UIE, goiter frequency and high TSH levels) and by indicators evaluating the degree of successfulness and sustainability of the salt iodization programs (sustainability indicators).

Indicators used to assess the iodine status of school-age children are median UIE, the prevalence of goiter determined by inspection/palpation or ultrasound, and the level of thyroglobulin (Tg).

Urinary iodine excretion (UIE) is a sensitive tool to indicate the present iodine status, being useful to evaluate the recent changes of iodine intake in the target population (Gorstein, 2001).

Median UIE (µg/L)	Iodine deficiency	Iodine intake
< 20	severe	insufficient
20-49	moderate	insufficient
50-99	mild	insufficient

Table 1. The degree of iodine deficiency in school-age children based on the median UIE, according to WHO classification (WHO et al., 2001).

The **frequency of goiter** (total goiter prevalence – TGP) reflects the population’s history of iodine nutrition but not its present iodine status, because thyroid size becomes normal for months or years after the correction of iodine deficiency. This indicator is useful to assess the severity of IDD at baseline and the long-term impact of control programs (de Benoist et al., 2004), but it is of limited usefulness in assessing the impact of programs once salt iodization has commenced (WHO et al., 2001).

Indicator	The degree of iodine deficiency		
	mild	moderate	severe
Prevalence of goiter assessed by inspection and palpation [%]	5-19.9	20-29.9	≥30
Frequency of thyroid volume >97th percentile by ultrasound* [%]	5-19.9	20-29.9	≥30
Mean serum Tg level [ng/mL]	10-19.9	20-39.9	≥40

*corresponding to the upper normal limit of thyroid volume

Table 2. The degree of iodine deficiency in school-age children based on goiter prevalence, according to WHO classification (WHO et al., 1994, 2001).

The screening of thyroid volume assessed by inspection and palpation may furnish subjective bias in as much as 30-40% of the cases (Delange, 1994; Gutekunst & Teichert, 1993; WHO et al., 1994; Vitti et al., 1994), being imprecise mostly for small goiters. Therefore, thyroid ultrasound (US) is a far better method to detect goiter in population, especially in children (Gutekunst & Teichert, 1993). It determines more accurately and objectively the thyroid size, but there is no agreement on reference values. The upper normal limit of thyroid volume in children living in normal iodine-supply regions was elaborated (Delange et al., 1997). In the following years the reevaluation of previous measurements and the standardization of values in iodine-deficient regions were suggest-

ed, because the values provided on the basis of data collected in Europe (Delange et al., 1997) were overestimated by 30% (Zimmermann et al., 2001). Reliable new values have been provided in iodine-sufficient school-children (Zimmermann et al., 2004).

A geographical region is defined as iodine-deficient if the median UIE is below 100µg/L or the prevalence of goiter is higher than 5% among school-age children (aged 6 to 12 years) (WHO et al., 2001).

The **serum TSH level** as an indicator of iodine status is particularly used in neonatal screening programs. A region is considered iodine-deficient if the frequency of serum TSH>5mIU/L is higher than 3% (WHO et al., 1994; 2001). In school-children the level of TSH measured together with free-thyroxine (FT₄) determines the thyroid dysfunction (subclinical or overt hypothyroidism) which has appeared in the context of iodine deficiency.

The major goal of IDD elimination programs is to ensure the sustained elimination of iodine deficiency. The sustainability is evaluated by median UIE, besides other sustainability indicators (the proportion of households consuming adequately iodized salt, and programmatic indicators, such as the effectiveness of public health authorities and salt industry to monitor and control the whole procession). Sustained elimination of iodine deficiency is ensured if the proportion of target population with UIE<100µg/L is under 50%, and of those with UIE<50µg/L is below 20% (WHO et al., 2001).

1.8. Iodine requirement, IDD prophylaxis in school-age children

The human body needs very small amount of iodine (in average 200µg/day), but the intake should be continuous. The recommended daily iodine intake varies by references. In 2001 the WHO/UNICEF/ICCIDD recommended 120µg/day iodine for school-children (6 to 12 years) and 150 µg for individuals above 12 years, but with these amounts the recommended UIE of 100-200µg/L was not obtained, reaching only 55-80µg/L. In addition to table salt, iodization of animal food and bottled table water can contribute to iodine intake (Andersson et al., 2007; Szybinski, 2011).

1.9. Current iodine status worldwide

Iodine deficiency continues to be a major public health problem in many parts of the world. World statistics show that 1.6 billion people are at risk of being affected by the reduced iodine in their diet, 50 million children are suffering of IDD and every year 100.000 children are born with cretenism worldwide. In 2002 a number of 14 countries of Western and Central Europe have reached a normal status of iodine nutrition, 3 countries were close to iodine sufficiency, but 13 countries, including Romania did remain with persisting IDD (Delange, 2002).

The WHO/UNICEF/ICCIDD report published in 2007 stated that 70% of the world population had access to iodized salt (Andersson et al., 2007), although only 41 countries worldwide can be classified as consuming adequate iodine. Using the median UIE of <100µg/L as the current indicator for insufficient iodine intake, 2 billion people remain at risk for iodine

deficiency (Andersson et al., 2007). The recent WHO/ICCIDD study on IDD carried out in 2011 showed that national surveys covered 114 countries, and since 2007 new data have been obtained from 74 countries. From these data it emerged that populations of 37 countries were still classified as iodine deficient, of which 9 had moderate and 28 mild deficiency. IDD in population show a declining tendency, from 54% in 2003 to 47% in 2007 and 37% in 2011. Corresponding results for school-age children were 36.5%, 31.5% and 30.5%, respectively. However, only 32% of these studies were carried out in known iodine deficient areas. In the European Union only 44% of population live in iodine sufficient areas (Andersson, 2011). The experience accumulated thus far has shown that the prevention and control of iodine deficiency requires monitoring to be sustainable.

Endemic cretinism as the most severe complication of IDD was practically eradicated as late as the second half of the 20th century by prophylactic programs conducted worldwide, but serious consequences of IDD are persisting and currently iodine deficiency still remained a major populational health problem.

The iodine status of Mureș County has not been evaluated since 2000. Similarly, the impact of universal salt iodization program initiated in 2003 was not studied in Mureș County. In 2006 we proposed to evaluate the outcome of universal salt iodization in school-age children from iodine-deficient regions of Mureș County, after the legislative changes targeting the improvement of iodine status in Romania were initiated.

2. Objectives

Our primary objective was to evaluate the impact of universal salt iodization (with increased KIO₃-content) at school-age children living in formerly iodine-deficient areas from Mures County (mainly from rural mountainous regions). Secondly, we proposed to assess the frequency and grade of endemic goiter, as well as of thyroid dysfunctions in children from these well known iodine-deficient regions. Additionally, we intended to diagnose other etiological factors of goiter and hypothyroidism, such as juvenile chronic autoimmune thyroiditis (Hashimoto's disease).

3. Material and methods

Material. The target population was school-age children, having 8-14 years of age of both sexes, living in mountainous rural localities of Mureș County known as iodine deficient regions in 1999-2000, before the implementation of universal salt iodization.

In October 2006 the team of endocrinologists from Endocrinology Clinic Târgu Mureș investigated 135 school-children (Vth-VIIIth classes) from three villages known as endemic areas in Gurghiu Valley: 55 children from Cașva, 30 from Glăjărie and 50 from Ibănești. The total population of these three localities is estimated by the censuses of population and housing realized in Romania in 2002: Cașva had 569, Glăjărie 1797 and Ibănești 2377 inhabitants.

The endocrinologists arrived to schools located in the mentioned geographical areas, and the children of classes between Vth-VIIIth were examined at the school's health room. This screening activity was previously planed, thus the children were told not to eat on the morning of investigations.

Locality	Mean age (years)	No. boys	No. girls	Total number
Caşva	11.51±1.89	34	21	55
Glăjărie	11.80±1.32	20	10	30
Ibăneşti	12.80±1.23	24	26	50
Total	12.05±1.64	78 (57.7%)	57 (42.3%)	135

Table 3. Mean age and gender distribution of school-children living in the studied mountainous villages of Mureş County

Methods. Data recording was completed with initials, age, gender, hight, weight, physical examination, laboratory and imagistic information for every child. In all cases physical examination and thyroid ultrasonography were performed, then urine and blood samples were collected in order to measure UIE, the level of TSH (thyrotropin), free-thyroxine (FT₄) and anti-thyroid peroxidase antibodies (TPO-Ab).

Samples of drinking water and alimentary salt accesible in the local food marts in every locality were collected in order to measure their iodine content.

Firstly family and personal history were taken, than physical examination and thyroid ultrasonography were performed.

Family history of thyroid dysfunctions, goiter, or any known thyroid disease of parents and other relatives was clarified. In the case of 82 children we could take a valuable familial anamnesis. Personal history of thyroid disease also was registered.

Physical examination consisted of general examination of organs and segments of the body, focusing on the possible signs and symptoms of thyroid disorders.

Anthropometric parameters were determined. *Height* and *weight* were measured and compared to the standard, being calculated the height-SDS and weight-SDS. Normal height and weight charts of Prader for both sexes from Switzerland reported in 1989 were used, as these are accepted for children living in Romania and similar charts adapted for the Romanian population are not available.

We distributed the casuistry in cohorts with/without hypothyroidism, with/without iodine deficiency, and the mean height and weight of the group was calculated, as well as the data between groups were compared by statistical means.

Local examination of the anterior and lateral cervical regions including the regional lymph nodes represents an important part of the investigation. Inspection and palpation of thyroid gland provided information about the size, consistency and surface of the thyroid, as well as

the existence of palpable thyroid nodules and cervical lymph node enlargement. Goiter was clinically defined according to the WHO criteria in 1960 for the classification of thyroid size (Perez et al., 1960). Goiter was diagnosed if its size was grade 1a (palpable thyroid lobes larger than the terminal phalanges of the subject's thumbs), grade 1b (visible with the extended neck), grade 2 (visible with the head in normal position, but the goiter does not extends beyond the medial edge of the sternocleidomastoidian muscles) or grade 3 (visible at a distance and it extends beyond the previous limits) (Perez et al., 1960). Nodules in the thyroid that is otherwise not enlarged fall into grade 1 category (Delange & Dunn, 2005). The inspection and palpation of the anterior and lateral cervical regions were effectuated at all school-age children included in our study.

Thyroid ultrasound (US) was performed in all cases by a portable instrument (Sono Ace 600 – SA-600) using a 7.5-MHz linear transducer. The volume of thyroid lobes was measured and the total thyroid volume was calculated. The structure of thyroid tissue and the presence/absence of thyroid nodules were also investigated.

The volume of each thyroid lobe was calculated by the formula: $V = \text{lenght} \times \text{width} \times \text{depth} \times 0.479$ (all values expressed in cm), than they were added together to obtain the total volume of the gland. The isthmus was ignored unless a nodule was present. In our study the volume of lobes was calculated automatically by the computer of the US equipment.

We evaluated our data according to values of ultrasound provided by the Thyromobil project performed in Europe (Delange et al., 1997 – Table 4.) and to data furnished by Zimmermann et al. (Zimmermann et al., 2004 – Table 5.) for all children with age between 6-12 years. The thyroid volume measured in 13-14 years-old adolescents was compared to values provided by Delange et al., 1997.

The measured thyroid volumes were also adjusted to the body surface area (BSA) and the obtained data were evaluated according to the upper normal limits (Table 5).

Body surface area was calculated using a variant of Dubois formula:

$$BSA \text{ (m}^2\text{)} = 0.007184 \times \text{Height(cm)}^{0.725} \times \text{Weight(kg)}^{0.425}.$$

After evaluation of thyroid volume for every children, the frequency and the grade of goiter was determined in the cohort.

Upper normal limit of thyroid volume (mL)										
Age (years)	6	7	8	9	10	11	12	13	14	15
Boys	5.4	5.7	6.1	6.8	7.8	9.0	10.4	12.0	13.9	16.0
Girls	5.0	5.9	6.9	8.0	9.2	10.4	11.7	13.1	14.6	16.1
BSA (kg/m²)	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7
Boys	4.7	5.3	6.0	7.0	8.0	9.3	10.7	12.2	14.0	15.8
Girls	4.8	5.9	7.1	8.3	9.5	10.7	11.9	13.1	14.3	15.6

Table 4. Age- and BSA-adjusted upper normal limit of thyroid volume measured by ultrasound for children living in iodine-sufficient areas (Delange et al., 1997).

Median P97 of thyroid volume (mL)										
Age (years)	6	7	8	9	10	11	12	13	14	15
Boys	2.91	3.29	3.71	4.19	4.73	5.34	6.03	-	-	-
Girls	2.84	3.26	3.76	4.32	4.98	5.73	6.59	-	-	-
BSA (kg/m ²)	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7
Boys	2.95	3.32	3.73	4.2	4.73	5.32	5.98	6.73	7.57	-
Girls	2.91	3.32	3.79	4.32	4.92	5.61	6.40	7.29	8.32	-

Table 5. Age- and BSA-adjusted median values (97th percentile – P97) for thyroid volume measured by ultrasound for children living in iodine-sufficient areas (Zimmermann et al., 2004).

The standards of normal thyroid volume according to age and BSA are very different in the references, so at last we evaluated our results on the basis of the values obtained in the region surrounding Iași, (in Moldova, eastern part of Romania) provided by the team of endocrinologists from Iași (Vulpoi et al., 2002; Zbranca et al., 2008).

Intellectual capacity of 59 children was evaluated by school performances provided by the school's teaching and medical staff. School performance spectrum was distributed into four subgroups: very good, good, mediocre and low capacity.

In order to measure **urinary iodine excretion** (UIE), the 24-hours urine was collected, than the whole urine quantity was mixed and a 50mL sample was retained and transported to the laboratory. Urinary iodine concentration was determined with the colorimetric procedure based on the Sandell-Kolthoff reaction, using ammonium persulfate (WHO et al., 2001; Dunn et al., 1993).

After obtaining absolute urinary iodine levels for individuals, mean and median UIE values were calculated for our studied groups.

Urinary iodine excretion measurement expressed in µg/L refers to the median value of the UIE calculated for the target population. We estimated the impact of universal salt iodization to eliminate iodine deficiency at school-age children by the interpretation of UIE based on WHO criteria (Table 1).

The assessment of **thyroid function** was also performed. Serum TSH, FT₄ and TPO-Ab levels were determined from 5 mL total blood collected by venipuncture into heparinized tubes.

Serum TSH and free-T₄ levels were measured from venous blood in the morning in all children included in the study. Third generation ECLIA (electrochemiluminescence immunoassay) was applied at the Central Laboratory of Emergency Clinical Hospital Mureș County. Normal range for TSH was considered between 0.27-4.2mIU/L and for FT₄ between 0.932-1.71ng/dL. We evaluated the presence and the severity of hypothyroidism, being diagnosed overt primary hypothyroidism in case of high TSH with reduced FT₄, and subclinical form if TSH was increased and FT₄ normal or at the lower normal limit.

The level of **anti-thyroid peroxidase antibodies** (TPO-Ab) was measured in every school-children. Values under 50IU/mL were considered normal. TPO-Ab above 50IU/mL indicates the presence of juvenile form of Hashimoto’s thyroiditis.

Iodine content of drinking water in each village in question was measured. Water samples were collected from the main fountains used by the majority of inhabitants in every localities, and from the water supply network in the school, respectively. These samples were processed by the Laboratory Unit Mureş of the Romanian Academic Research Institute. The iodine-concentration of water under 50µg/L was considered low.

Iodine content of alimentary salt available in the local food marts was also determined. According to the legislative measures the iodine content of the salt must be between 25.5-42.5mg/kg of potassium iodate (KIO₃).

The collected data were systematised and statistically processed. The parameters between groups were compared statistically with T-Student test and Chi-square-test. Homologue parameters between the groups were considered statistically different, if P-value<0.05.

4. Results

Anthropometric parameters of the 135 school-age children living in the three studied mountainous villages (Caşva, Glăjărie, Ibăneşti,) show similar distribution (Table 6.). From the whole cohort 6 children had height below --2SD (mean -2.27±0.24).

Family history was positive for thyroid disturbances (including goiter) in 11 children from the 82 cases with precise data (13.4%). A proportion of 54.5% of children (6/11) with positive family history presented goiter and/or hypothyroidism vs. 32.4% (23/71) of individuals without family history for thyroid condition. The difference between the groups was not significant (P-value: 0.18, OR: 2.50, 95%CI: 0.69-9.07).

Parameter	Studied villages from Mureş County			whole cohort
	Caşva	Glăjărie	Ibăneşti	
Mean W-SDS [SD]	+0.13±1.06	+0.32±1.18	-0.11±1.20	+0.08±1.15
Minimum W-SDS [SD]	-2.26	-2.58	-2.88	-2.88
Median W-SDS [SD]	-0.06	+0.34	+0.005	+0.18
Maximum W-SDS [SD]	+3.18	+2.44	+2.79	+3.18
Mean H-SDS [SD]	-0.10±0.98	+0.07±1.10	+0.02±1.05	-0.01±1.03
Minimum H-SDS [SD]	-2.28	-2.72	-2.30	-2.72
Median H-SDS [SD]	-0.04	+0.005	+0.18	0.00
Maximum H-SDS [SD]	+2.33	+2.20	+2.43	+2.43

W- and H-SDS: weight and height standard deviation score

Table 6. Anthropometric parameters of school-age children living in mountainous villages from Mureş County

Physical examination of the anterior and lateral cervical regions has shown a 51.1% overall goiter frequency. In all cases diffuse goiter was palpable. In more than half of the cases only small goiter (grade Ia) was present, and goiter grade II was met very rarely (6.7% of all children).

Locality	Number of cases	Thyroid size on physical examination				Overall goiter frequency
		Grade 0	Grade Ia	Grade Ib	Grade II	
Cașva	55	56.4% (31/55)	27.3% (15/55)	10.9% (6/55)	5.4% (3/55)	43.6% (24/55)
Glăjărie	30	53.3% (16/30)	26.7% (8/30)	16.7% (5/30)	3.3% (1/30)	46.7% (14/30)
Ibănești	50	36% (18/50)	30% (15/50)	22% (11/50)	10% (5/50)	62% (31/50)
Total	135	48.1%	28.1%	16.3%	6.7%	51.1%

Table 7. The distribution of thyroid size according to WHO classification

Thyroid volume assessment by ultrasound Thyroid ultrasound was performed in every child enrolled in our study in 2006, the data regarding thyroid volume were calculated in function to age and BSA (Tables 8. and 9.).

Age [years]	Subjects [number]	Thyroid volume [mL]			
		Min.	Max.	Median	Mean
8	5	2.77	5.23	3.16	3.67±1.04
9	7	3.18	4.87	3.67	3.82±0.63
10	10	4.11	10.24	5.29	5.82±1.77
11	24	3.62	8.37	6.36	6.01±1.61
12	26	2.65	21	5.71	6.46±3.42
13	33	4.45	16.04	7.86	8.42±3.09
14	30	3.61	13.18	7.73	8.17±2.47

Table 8. Age-related minimum, maximum, median, and mean thyroid volume measured by ultrasound in the investigated school-children

BSA [m ²]	Subjects [number]	Thyroid volume [mL]			
		Min.	Max.	Median	Mean
0.8	1				2.77
0.9	1				7.15
1.0	11	2.95	9.03	4.66	4.70±1.64
1.1	17	3.18	6.80	4.87	4.78±1.01
1.2	24	2.65	9.02	5.34	5.78±1.89
1.3	18	3.15	11.78	6.71	7.29±2.38
1.4	30	3.62	14.80	6.78	7.06±2.83
1.5	19	5.60	14.55	7.61	8.86±2.69
1.6	5	6.62	9.41	7.85	7.93±1.01
1.7	9	7.17	21.00	10.73	11.80±4.39

Table 9. BSA-related minimum, maximum, median, and mean thyroid volume measured by ultrasound in the investigated school-children

The thyroid volume of every child was compared to data furnished by Delange et al. in 1997 and Zimmermann et al. in 2004 (see Tables 4. and 5.), then the frequency of goiter in the studied villages from Mureș County was determined.

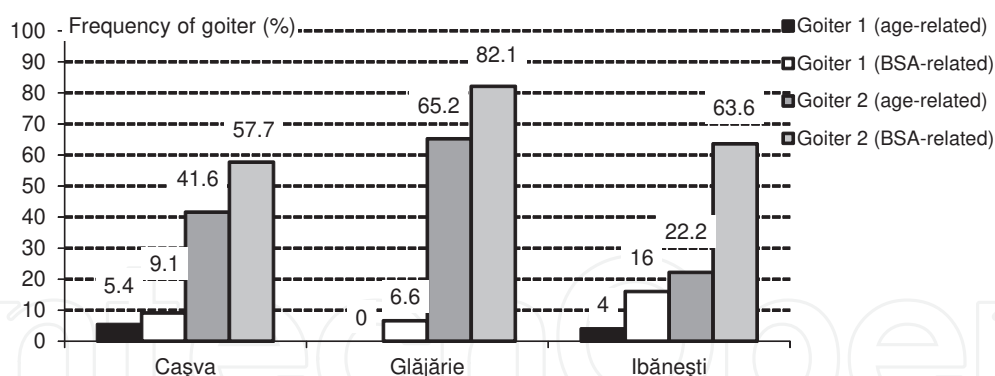


Figure 1. The frequency of goiter in school-children living in mountainous villages from Mureș County, Romania. Goiter 1 – the results evaluated according to Delange et al. 1997; Goiter 2 – the results were classified corresponding to data of Zimmermann et al. 2004.

Figure 1. shows a very variable goiter frequency according to the used standards, being situated between 5.4-57.7% in Cașva, between 0-82.1% in Glăjărie and between 4-63.6% in Ibănești. Evaluation of our results based on the normal values provided by Iași County, a formerly iodine-deficient Romanian region (Zbranca et al., 2008), shows that goiter was detected in 9 (16.3%) children living in Cașva, in 4 (13.3%) school-children from Glăjărie, and in 14 (28%) subjects from Ibănești.

The frequency of goiter in the whole investigated group was 20% (27 children from the total number of 135 cases), compared to standards provided by Vulpoi et al., 2002, Zbranca et al., 2008. All cases of goiter were diffuse.

The frequency of goiter assessed by physical examination and ultrasound were compared, and distributed regarding to gender. The overall goiter frequency provided by ultrasound was significantly higher in girls than in boys (28% vs. 14.1%). Thyroid enlargement was almost similar in both sexes in the subgroup from Cașva, twice and more than three times higher in girls from Glăjărie and Ibănești, respectively, although stratified data according to localities show non-significant differences between the subgroups (Table 10).

Locality	Frequency of goiter assessed by physical examination		Frequency of goiter assessed by ultrasound	
	Girls	Boys	Girls	Boys
Cașva	47.6% (10/21)	41.1% (14/34)	14.2% (3/21)	17.6% (6/34)
	Not significant (NS)		Not significant (NS)	
Glăjărie	50% (5/10)	45% (9/20)	20% (2/10)	10% (2/20)
	NS		NS	
Ibănești	73% (19/26)	50% (12/24)	42.3% (11/26)	12.5% (3/24)
	NS		NS	
Total	59.6% (34/57)	44.8% (35/78)	28% (16/57)	14.1% (11/78)
	P:0.11, RR:1.32, 95%CI:0.959-1.841		P:0.052, RR:1.99, 95%CI:1.001-3.959	

Table 10. Gender distribution of frequency of goiter assessed by physical examination and thyroid ultrasound

We divided the cohort in two groups according to age: one group with children between 6-12 years (72 cases) and the other with subjects between 12-14 years (63 cases). The frequency of goiter assessed by physical examination in the first group was 40.2% (29/72) with no difference between sexes (48.2% in girls and 41.8% in boys), and 58.7% (37/63) in the second group with difference almost significant between sexes (71.4% in girls and 48.5% in boys, P: 0.078, OR: 2.64, 95%CI: 0.9221-7.599).

Urinary iodine excretion measurement

In 2006, at about 2-2.5 years after the implementation in practice of universal salt iodization the mean UIE of the 135 children living in the three mentioned villages from Gurghiu Valley was $85.37 \pm 60.05 \mu\text{g/L}$. The median UIE of $74.88 \mu\text{g/L}$ indicates globally a mild iodine deficiency, but stratified data show large interindividual variations within children.

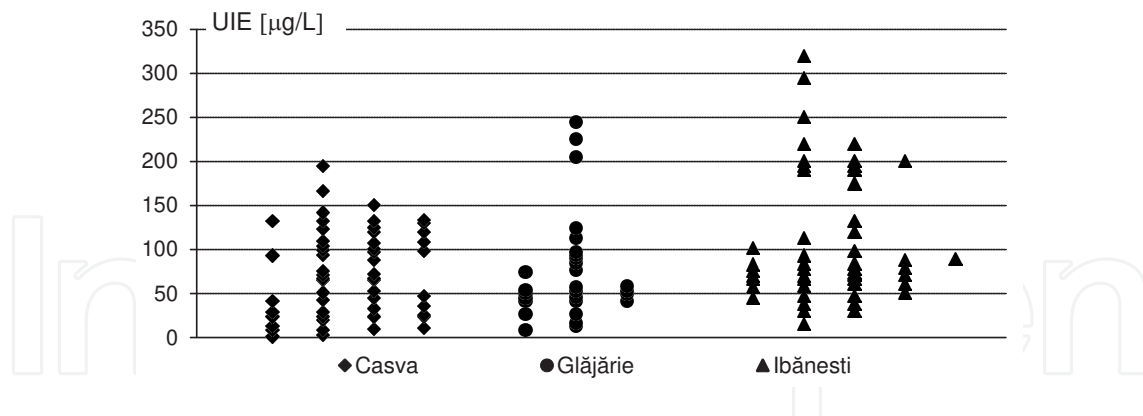


Figure 2. Distribution of individual values of UIE in school-children living in the three studied villages from Mureş County in 2006

UIE below normal range was detected in 68.1% of the cohort. The proportion of UIE <50µg/L reached 30.3%, and that of UIE <100µg/L was 68.1%, which are above the maximal values (20% for UIE <50µg/L and 50% for UIE <100µg/L) of adequate iodine-supply conditions. A large part of the group (60.9%) had mildly or moderately low UIE.

Indicators of iodine status	Data from the studied villages			Whole cohort
	Caşva	Glăjărie	Ibăneşti	
Mean UIE [µg/L]	72.91	75.42	117.84	85.37
Median UIE [µg/L]	67.00	53.50	81.00	74.88
Mean UIE ± SD [µg/L]	72.91±48.63	75.42±60.30	117.84±91.95	85.37±60.05
Frequency of cases with UIE<100µg/L [%]	67.3 (37/55 cases)	76.6 (23/30 cases)	64 (32/50 cases)	68.1 (92/135)
Frequency of cases with UIE<50µg/L [%]	40 (22/55 cases)	36.6 (11/30 cases)	16 (8/50 cases)	30.3 (41/135)
Frequency of goiter assessed by US [%]	16.3 (9/55 cases)	13.3 (4/30 cases)	28 (14/50 cases)	20 (27/135)

Table 11. The indicators of iodine status and of universal salt iodization program sustainability in school-children from mountainous villages in 2006

Thyroid function. In the whole group mean TSH level was 2.32±1.04mIU/L and mean FT₄ concentration 1.07±0.12ng/dL. These values are situated in the normal range, but individual hormonal results showed primary hypothyroidism in 24 (17,7%) children. Fifteen of them had mild overt hypothyroidism and 9 subclinical form, the mean TSH being 5.28±0.73mIU/L (normal: 0.27-4.2) and mean FT₄ 0.86±0.05ng/dL (normal: 0.932-1.70).

In Caşva the mean TSH was normal (2.34±1.00mIU/L). Nine (16.3%) children had primary hypothyroidism. In Glăjărie the mean TSH and FT₄ were also normal (2.12±0.93mIU/L and 1.08±0.13, respectively), and 5 school-children (16.6%) were detected with hypothyroidism

(4 mild overt and 1 subclinical form). In Ibănești 10 subjects (20%) were diagnosed with thyroid insufficiency (6 mild overt and 4 subclinical).

We did not detect any case of hyperthyroidism.

TPO-Ab was negative (<50IU/mL) in all 135 cases, which means that juvenile chronic autoimmune thyroiditis was not met in this cohort, and hypothyroidism was not caused by this thyroid disease, rather it was induced by iodine deficiency.

We did not found considerable or significant differences of somatic development in children with or without iodine-deficiency, with or without hypothyroidism.

Intellectual performances of 59 children were recorded, and then we distributed them into two groups: one (1. subgroup) with children having mediocre and low learning capacity (32 cases), and the other (2. subgroup) consisting of individuals with good or very good performances (27 cases). The goiter frequency based on ultrasound was 22.5% in the first, and 17.8% in the second group (P-value >0.05). We compared the mean UIE, TSH and FT₄ between the subgroups of children with different school performances, but we did not found significant differences, excepting a tendency of reducing school performances with the gradually increasing values of TSH and decreasing levels of FT₄ (Figure 3.).

Our results recorded in 2006 show that the **water sample** from Cașva contains 3.8μg/L iodine, and the iodized alimentary salt 16.02mg/kg (which was lower than the ordered concentration of 34±8.5mg/kg). In Glăjărie the iodine content of the water from the central fountain was 1.0μg/L, from the parish yard 1.9μg/L, in the running water from the school 0.45μg/L and from the medical unit 4.2 μg/L. The iodine content of water from Ibănești was 0.6μg/L and of the iodized alimentary salt 51.64mg/kg (which was higher than the allowed upper normal concentration).

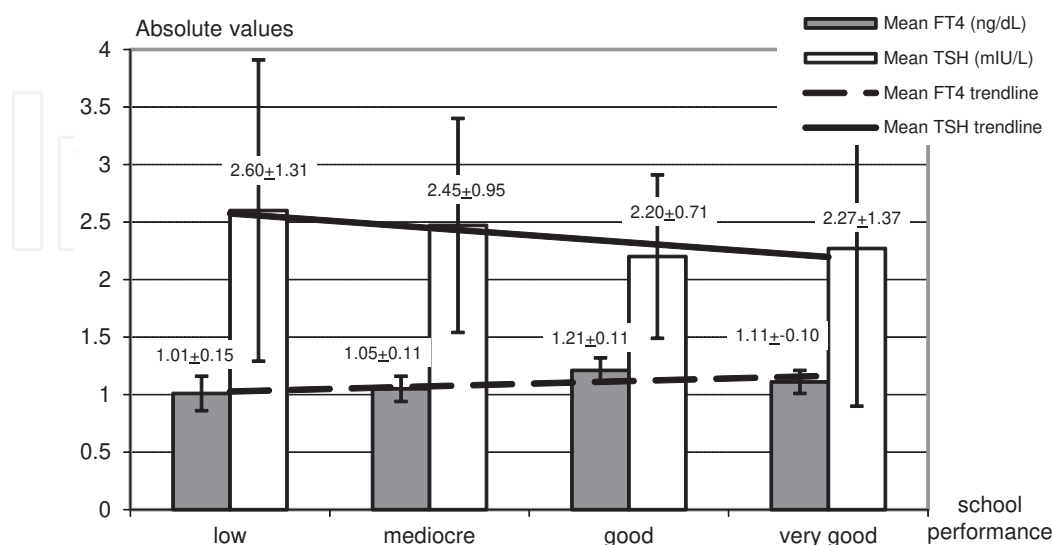


Figure 3. The mean TSH and FT₄ levels in subgroups of children distributed according to school performances

5. Discussion

In 2003 the Romanian governmental decision regarding universal salt iodization was implemented into practice, and in 2006, after about 2.5-3 years, we evaluated the impact of this program in regions of Mureș County known as moderate or mild iodine deficient.

In order to evaluate the impact of universal salt iodization program in Romania in the context of national strategy on the elimination of iodine deficiency disorders from 2003, we compared our results reflecting iodine status in localities from Mureș County after the implementation of this program with those before it. Thus, we compared the indicators of iodine status in Mureș County reported in 1998-1999 by Balázs et al. (1998; 2000/a; 2000/b), before the governmental measures, with the same indicators measured by us in 2006. The mentioned data in 1998/99 were obtained in the superior and middle hydrographic basin of the Mureș river, investigating a group of 508 school-children living in areas surrounding locality Deda (situated in a mountainous region in Mureș County). From the 508 school-age children 26.97% (137 cases) were living in urban and 73.03% (371) in rural localities.

Physical examination of thyroid gland by palpation and inspection was performed in both studies (in 1998/99 and in that presented now). Thyroid size determined by local physical examination was evaluated according to WHO criteria (0, Ia, Ib, II, III subgroups) in the mentioned former studies. According to the Bourdoux classification the volume of thyroid gland was enlarged by palpation in 45.27% of children: grade Ia goiter observed in 29.92% (152 cases), grade Ib in 14.17% (72), and grade II in 1.18% (6 children). Those studies highlighted the high frequency of low grade goiter in rural localities in comparison with a lower frequency observed in urban regions (Balázs et al., 1998).

In the present work physical examination shows an overall goiter frequency of 51.9%, prevailing small goiters (grade Ia) in all studied villages (more than half of goiters), large goiters being very rare (grade II only in 6.7% of all cohort). Comparing the data of the two series we could not found any improvement in the overall frequency of goiter (45.28% in 1999 vs. 51.1% in 2006), but we must take into account, that in the previous study children came from several localities (including Târgu Mureș, the capital city of Mureș County) with different iodine status (mild or moderate iodine deficient, as well as with normal iodine supply). A considerable number of the enrolled children were from Târgu Mureș, a city which proved to be without iodine deficiency. In the present work we focused on mountainous villages, known before as iodine deficient regions, some of them (Cașva and Glăjărie) known partly isolated in socioeconomical and geographical point of view.

In our study physical examination of thyroid gland shows variable goiter frequency in the three localities: it is the highest in Ibănești (62.0%) vs. the other two localities (46.7% in Glăjărie and 43.6% in Cașva). This result is not in concordance with the fact that Ibănești is the largest among the three localities, with better socioeconomical status and lesser isolated. An explanation might reside in the differences in age, gender and pubertal stage of the children. In Ibănești the mean chronological age of school-age children enrolled in the study is higher (12.05 years vs. 11.51 and 11.80 years in the other

two localities), and the distribution between sexes is almost 1:1 (differing evidently from boys:girls-ratio of 2:1 in Glăjărie and 3:2 in Cașva). Taking into account that the girls from Ibănești were older, between 12-14-years, the pubertal stage was higher in this group. Balázs et al. (1998) have reported the increased incidence of grade Ib and II goiter in children with pubertal onset compared to those being in prepubertal stage, as pubertal onset is an important facilitating factor for goiter development. This is in concordance with our data, too, related to gender. The overall goiter frequency provided by ultrasound was significantly higher in girls than in boys (28% vs. 14.1%): although goiter appeared almost with the same frequency in both sexes from Cașva (14.2% in girls and 17.6% in boys), but it was more than 3-times more frequent in girls than in boys living in Ibănești (42.3% vs. 12.5%). Euthyroid pubertal goiter is especially frequent in adolescents, because iodine metabolism is accelerated during this period of life (Delange & Ermans, 1967).

Then we compared our data obtained in 2006 to the results recorded during April-June 1999 at school-age children living in Deda, a mountainous rural locality, presumed as iodine deficient area. In that study 36.22% of the children had goiter, mainly of small size, without considerable differences between the sexes (Balázs et al., 2000/a) – the goiter being assessed by inspection/palpation. This result is similar to that in the present study (40.2% in children with age between 6-12 years), without any significant differences between the groups. It must be emphasized, that the lack of gender differences may be attributed to inspection/palpation method for the diagnosis of goiter. Taking into account the subjectivity and bias of physical examination of thyroid gland, especially in young children, as this method of evaluation estimates goiter presence with an error as much as 30-40%, our interpretation was based mainly on thyroid ultrasound.

The objective determination of thyroid volume by ultrasound provided the exact size of the thyroid, however it was difficult to choose the adequate standards for the normal thyroid volume fitting to the goiter estimation in our region. The references published during the last 2-3 decades provide very variable standards for the upper normal limit of thyroid ultrasound volumetry adjusted for age, gender and BSA.

We evaluated firstly the age- and BSA-adjusted goiter frequency compared to the reference values provided by the Thyromobile survey across Europe (Delange et al., 1997), and thereafter we reevaluated the results according to parameters published by Zimmermann (2004), but we obtained very different results (Figure 1.). After all we chose the standards provided by a team of endocrinologists from Iași performed on a cohort living in a formerly iodine deficient Romanian region (Vulpoi et al., 2002; Zbranca et al., 2008). Thus, goiter frequency in our cohort assessed by ultrasound was 20%, with a considerable difference between the sexes (28% in girls and 14.1% in boys).

In the study of Balázs et al. (2000/a) thyroid ultrasonography was also performed in 83 children living in Târgu Mureș. The mean thyroid volume determined by ultrasound among these children was $5.22 \pm 1.51 \text{ cm}^3$, adjusted to a mean body surface area of $1.23 \pm 0.14 \text{ m}^2$. Goiter evaluated by ultrasound was detected in 33.73% of the children, mainly small goiters (grade Ia), predominantly in girls (about 2/3 in girls and 1/3 in boys).

The 20% of goiter frequency (diagnosed by ultrasound) detected in school-age children by us, reflects a mild/moderate iodine deficiency in the studied three mountainous villages from Mureș County in 2006. The stratified results of each locality showed that Cașva and Glăjărie were mildly iodine deficient areas (reflected by 16.3 and 13.3% goiter, respectively), and Ibănești moderately iodine deficient (with 28% goiter).

So, we observed a significant reduction of goiter frequency after the measures taken in the frame of universal salt iodization, compared to the results obtained by Balázs et al. in 1998/99 (the overall goiter frequency 20% in 2006 vs. 33.73% in 1999 – P-value: 0.025, RR: 1.687, 95%CI: 1.073-2.652). As thyroid enlargement reflects the former iodine status, i.e. the history of iodine nutrition for the previous several months/1-2 years, this means a significant improvement of iodine status in the studied regions, reflecting the beneficial outcome of universal salt iodization.

Urinary iodine excretion reflects the present iodine status of a geographical region. Determination of UIE with Sandell-Kolthoff reaction, using ammonium persulfate was the laboratory method used in the both series of study (realized in 1998/99 and in 2006) performed in Mureș County, so the absolute values could be compared.

In 1998/99 the majority of rural localities situated on the superior and middle hydrographical basin of the river Mureș were mildly iodine-deficient areas, the rest being moderately deficient. The mean UIE was $100.22\mu\text{g/L}$, but with a high interindividual variation: $\text{SD} \pm 73.37$ (Balázs et al., 1998). The mountainous rural region of Deda was considered moderately iodine deficient in 1998, the normal UIE being detected only in 6.9% of cases, and the mean UIE being $59.95 \pm 30.22\mu\text{g/L}$. Although in Târgu Mureș the mean UIE was within the normal range ($130.05 \pm 75.45\mu\text{g/L}$), normal individual UIE levels $>100\mu\text{g/L}$ were observed only in 56.79% of the children (Balázs et al., 1998; 2000/a; 2000/b).

In 2006, at about 2-2.5 years after the implementation in practice of universal salt iodization the mean urinary iodine excretion measured in the 135 school-age children living in the three mentioned villages from Gurghiu Valley was $85.37 \pm 60.05\mu\text{g/L}$. Median value of $74.88\mu\text{g/L}$ indicates an overall mild iodine deficiency. In order to compare this result with that from 1999, the median UIE in 1999 was calculated based on the mean UIE in 1999 ($59.95 \pm 30.22\mu\text{g/L}$) using the formula recommended by WHO (median UIE = $1.128 + 0.864 \times \text{mean UIE}$ – WHO et al., 2001). Thus, the estimated median UIE was $52.29\mu\text{g/L}$ before the universal salt iodization program.

The median UIE compared to the previous studies shows also a considerable improvement in the iodine status of rural regions from Mureș County, being in concordance with the significant reduction of goiter frequency discussed previously. So, we observed better median UIE in Ibănești ($81.00\mu\text{g/L}$), in contrast with Glăjărie, known as the most isolated and with less socioeconomical background (having the lowest median UIE: $53.50\mu\text{g/L}$).

In the studies performed before universal salt Iodization highly variable interindividual UIE concentrations were observed, although the mean value indicated only a mild iodine deficiency. Normal UIE was found only in 6.9% of school-age children, which means a frequency of cases with $\text{UIE} < 100\mu\text{g/L}$ of 93.1%. In 2006 a large proportion (68.1%) of studied school-children had still mildly or moderately low UIE. Similarly to the studies

performed in 1998/99, the results of the present work show large interindividual variations of UIE (SD: $\pm 60.05 \mu\text{g/L}$).

Values below normal range (UIE $<100 \mu\text{g/L}$) were detected in 68.1% of our cohort, which is improved compared to data obtained in 1998/1999. Indeed, the proportion of cases with normal UIE has increased significantly in 2006 compared to that determined in 1998/1999 (31.9% vs. 6.9%, $P\text{-value} < 0.0001$, RR: 1.268, 95%CI: 1.183-1.581). However, this increase has not attained yet the most important criteria of normal iodine-supply conditions, i.e. the maximal value of 50% UIE $<100 \mu\text{g/L}$ (the 68.1% is still above of this limit with 18.1%); similarly, in our present study the proportion of UIE $<50 \mu\text{g/L}$ is 30.3%, for normal iodine-supply it must be $\leq 20\%$. These results show that the universal salt iodization program could not be ensured at an optimal level, being not sustained continuously.

The iodine status of the studied localities from Mureş County in 2006 was evaluated by the following indicators: median UIE for the current iodine status, frequency of goiter assessed by ultrasound for the history of iodine nutrition of the previous months-years, and the frequency of UIE concentrations below $100 \mu\text{g/L}$ and below $50 \mu\text{g/L}$ for the sustainability of universal salt iodization program (Table 12.).

Interpretation of indicators	Data from every studied villages			Whole cohort
	Caşva	Glăjărie	Ibăneşti	
Current iodine status in 2006 (by median UIE)	mild iodine deficiency	mild iodine deficiency	mild iodine deficiency	mild iodine deficiency
Former iodine status (before 2006) (by frequency of goiter)	mild iodine deficiency	mild iodine deficiency	moderate iodine deficiency	mild/moderate iodine deficiency
Sustained elimination of iodine deficiency (by % cases with UIE $<100 \mu\text{g/L}$ and UIE $<50 \mu\text{g/L}$)	not ensured	not ensured	not ensured	not ensured

Table 12. The interpretation of indicators showing the iodine status among school-children in the three mountainous villages in 2006

During 2006 the frequency of goiter in school-age children was 20% which is improved to that observed in 1998/99 (33.73%), but it has not reached normal levels yet, being situated at the borderline between mild and moderate iodine deficiency (5-19.9% and 20-29.9%, respectively). Our results show an improved iodine status in 2006: the mean UIE rose to $85.37 \pm 60.05 \mu\text{g/L}$, median UIE to $74.88 \mu\text{g/L}$, and 30.8% of children had normal urinary iodine excretion. Analysing separately the groups in every village, the mean UIE are different in some degree: $72.91 \pm 48.63 \mu\text{g/L}$ in Caşva, $75.42 \pm 60.30 \mu\text{g/L}$ in Glăjărie and $117.84 \pm 91.95 \mu\text{g/L}$ in Ibăneşti. Median UIE has improved compared to the situation in 1998/99, but it remained at subnormal levels, indicating a mild iodine deficiency in all three villages. The indicators for the estimation of sustained elimination of iodine deficiency were at subnormal levels. Studies performed during 2002-2004 reported an im-

provement of overall median UIE in school-age Romanian children from 70 (in urban) and 60 µg/L (in rural areas) in 2002 to 105 and 100 µg/L, respectively, until 2004. At the Second National Conference for the elimination of IDD held at Bucharest in 2005, the Mother and Child Care Institute "Alfred Rusescu" reported that in children of 6-7-years of age the overall iodine status tended to normalize, the median UIE reaching 100 µg/L (Stănescu, 2005). Although the median UIE became almost normal (105 in urban and 100 µg/L in rural localities), a large interindividual variation were found, reflected by the SD of ± 60 µg/L (Stănescu, 2005). Important differences between iodine status of rural and urban environment were observed. Mild iodine deficiency was recorded in 33.5% of the population, 11% presented moderate and 2.4% severe forms (Stănescu, 2005), although 96.3% of the households used iodized salt. These results could derive from the facts that more than half of the families used salt with inadequate iodine content (under 15 mg iodine/kg salt), 3/4 of the families consumed iodized salt but in an inadequate manner (adding salt before and during cooking) which reduces the content of iodine; the frequency of iodized salt consumption is higher in families with the higher educational level of the mother.

In conclusion, on the basis of the indicators for iodine status the mountainous villages located in Mureş Conty, known as mild/moderate iodine deficient regions in 1999, remained in the same iodine deficiency category during 2006, however the absolute values of indicators were considerably, some even significantly improved. The indicators situated before at the lower limit of mild/moderate iodine deficiency interval, after-wise were shifted to the middle zone and upper limit of this range. The universal salt iodization had a beneficial impact on iodine deficient rural regions, as expected, but its sustainability must be maintained, i.e. the effectiveness of public health authorities and salt industry to monitor and control the whole procession must be consolidated. The elimination strategy of IDD in mountainous rural areas remains a very important public health program, as the iodine content of water and soil is very low here. Water samples taken from the main water-provision points from every village showed that the iodine content of drinking water was very low in every locality, as expected in mountainous rural regions. Thus general measures to increase the iodine content of the water should be applied. The iodine content of the running water measured in 1998/99 and 2006 was very variable (the mean value being $X=10.15$ µg/L, $SD\pm 9.85$ – Balázs et al., 1998), but in all cases the iodine concentration was much more under the accepted value (levels above 50 µg/L being considered normal). Iodine content of alimentary salt found at the market of the three villages was in some cases under the prescribed level of 34 ± 8 mg/kg. The usage of iodized alimentary salt in households reached 96% in 2004 compared to 53% in the previous years (Goldner, 2005; Stănescu, 2005), but the alimentary salt was insufficient iodized (in 63% of cases, Goldner, 2005). A proportion of 74.5% of the sample of salt tested which was used in the market and for the panification had a standard iodine content of 15-25 mg/kg (Goldner, 2005), which was under the prescribed concentration. In spite of existent legislation to mandatory sale of iodized table salt on the market, about 12% of population consumes not iodized salt (Nanu, 2005), especially in rural environment.

The persistence of moderate iodine deficiency in some zones of Romania was attributed to the insufficient iodization level of the salt and waste during storage, to the uncontrolled selling of industrial salt as alimentary salt, to the lack of control measures in import of salt, to the inadequate monitoring system and the lack of efficient measures to realize entirely the governmental decision, as well as the resistency of alimentary industry (e.g. meat processing industry) to utilize iodized salt (Goldner, 2005).

We must remark the presence of hypothyroidism related to iodine deficiency in 17.7% of the investigated school-children, TPO-Ab being normal in all of them. Although, all cases of hypothyroidism were mildly overt or subclinical forms (15 and 9, respectively), we must take into account that even mild iodine and thyroid hormone deficiencies conduct to psychoneurological damages, the characteristic complication of latent deficiency being AD-HD syndrome in developed countries. Chronic iodine deficiency leads to suboptimal intellectual development. Recent studies performed in the European countries, known with iodine prevention programs initiated decades ago, and though that iodine deficiency was eliminated, sustain surprisingly the presence of mild iodine deficiency in many countries and implication of this in school performances, psychological and neurological status. These mild deficits probably results from transient hypothyroidism during the first 2-years of life, i.e. during the critical period of brain development (Delange, 2002). Besides iodine deficiency, an increase in iodine intake can also lead to a small but significant increase in the incidence of hypothyroidism, probably attributable to autoregulation of thyroid function.

In conclusion, the rural mountainous zones of Mureş County known before as moderate/mild iodine-deficient areas, became *mild-deficient*, due to the new measures of iodine prevention. In these areas universal salt iodization is not sufficient, being necessary to apply periodically special prophylactic measures (iodine tablets), too, primarily to prepubertal and pubertal children.

6. Conclusions

This work underlines considerable improvement of iodine nutrition in mountainous rural regions of Mureş County after the implementation in practice of universal salt iodization in Romania since 2003, although these areas remained mildly (some moderately) iodine deficient at about 2.5-3 years after the IDD elimination strategy was initiated. On one hand the prophylactic measures with higher iodine content of alimentary salt (KIO_3 25.5-42.5mg/kg) might not be sufficient for the full correction of iodine deficiency in these isolated mountainous rural regions, on the other hand special attention is required to monitorize continuously the market and reaching programs, as well as the sustainability of the prophylactic program must be ensured. In these areas special measures, i.e. iodine supplementation to the high-risk populational groups are periodically required in addition to universal salt iodization, especially as iodine deficiency occurred with hypothyroidism in 17.7% of school-children. The elimination of mild-moderate iodine deficiency in school-age children living in mountainous rural localities presumes special measures by the daily administration of 0.1-0.2 mg iodine tablets.

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References

- [1] Andersson M, de Benoist B, Darnton-Hill I, Delange F (2007) WHO, UNICEF: Iodine Deficiency in Europe: A continuing public health problem. World Health Organization, Switzerland, 1-70.
- [2] Andersson M (2011) Regional and Global Prevalence of Iodine Deficiency and Burden of Disease Due to Iodine Deficiency. West Central Europe Regional ICCIDD Satellite to 35th Annual ETA Meeting. In: Paschke R & Smyth P (eds.) *Thyroid International* 5: 14.
- [3] Balázs J, Vasilescu Gh, Buksa C, Pinte A, Gliga C, Alexandrescu C, Pașcanu I, Radu C, Balázs A, Puskás A (1998) Gușa endemică, carența de iod, condiția social economică și indicii de dezvoltare somatometrică și pubertară la școlari din localități situate în bazinul hidrografic al Mureșului superior și mijlociu (in Romanian). *Revista de Medicină și Farmacie* 44(Suppl. 3): 10-11.
- [4] Balázs J, Pinte A, Buksa C, Vasilescu G (2000/a) Volumul tiroidian și aportul de iod la copii de vârstă școlară din Târgu-Mureș – The thyroid volume and iodine intake in school-children from Târgu-Mureș (in Romanian). *Revista de Medicină și Farmacie* 46: 60-63.
- [5] Balázs J, Kun IZ, Buksa C, Coroș L, Vasilescu G, Năsălean A (2000/b) Studiul privind gușa endemică, tiroidita cronică, funcția tiroidiană în contextul aportului iodat, la elevi dintr-o localitate de pe cursul superior al Mureșului – Study of endemic goiter, chronic thyroiditis, thyroid function in correlation with iodine intake at school-children living in the superior hydrographic basin of the river Mureș (in Romanian). *Revista de Medicină și Farmacie* 46: 240-244.
- [6] Bernal J (2005) Thyroid hormones and brain development. *Vitamins and Hormones* 71: 95-122.
- [7] Bleichrodt N, Born MP (1994) A meta-analysis of research on iodine and its relationship to cognitive development. In: Stanbury JB (ed.) *The damaged brain of iodine deficiency*. New York, Cognizant Communication: 195-200.
- [8] Boyages SC (1994) Primary pediatric hypothyroidism and endemic cretinism. *Current therapy in endocrinology and metabolism* 5: 94-98.

- [9] Brook Charles DG, Brown Rosalind S (2008) Handbook of clinical Pediatric Endocrinology. Blackwell Publishing, Oxford.
- [10] Cornea GH (1957) Distrofia endemică tireopată pe valea Mureșului, de la izvor până la Târgu-Mureș (in Romanian). In: Milcu SM (ed.) Gușa endemică Editura Academiei, Vol I: 197-201.
- [11] de Benoist B, Andersson M, Egli I, Takkouche B, Allen H (2004) Iodine status worldwide. WHO Global Database on Iodine Deficiency. Department of Nutrition for Health and Development World Health Organization Geneva 2004.
- [12] Delange F (1994) The disorders induced by iodine deficiency. *Thyroid* 4: 107-128.
- [13] Delange F (2000) Endemic cretinism. In: Braverman LE, Utiger RD (eds.) The thyroid. A fundamental and clinical text. 8th Edition. Philadelphia, Lippincott, 743-754.
- [14] Delange F (2001) Iodine deficiency as a cause of brain damage. *Postgraduate Medical Journal*: 77:217-220.
- [15] Delange F (2002) Iodine deficiency in Europe anno 2002. *Thyroid International* 5: 1-18.
- [16] Delange FM, Dunn JT (2005) Iodine deficiency. In: Braverman LE, Utiger RD (eds.): Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text. Ninth Edition. Lippincott Williams & Wilkins, Philadelphia 264-283.
- [17] Delange F, Ermans AM (1967) Le métabolisme de l'iode à la puberté. *Rev Fr Etud Clin Biol* 12: 87-92.
- [18] Delange F, Benker G, Caron Ph, Eber O, Ott W, Peter F, Podoba J, Simescu M, Szybinsky Z, Vertongen F, Vitti P, Wiersinga W, Zamrazil V (1997) Thyroid volume and urinary iodine in European school-children: standardization of values for assessment of iodine deficiency. *Eur J Endocrinol* 136: 180-187.
- [19] Delange F, Robertson A, McLoughney E, Gerasimov G (1998) Elimination of iodine deficiency disorders (IDD) in central and eastern Europe, the Commonwealth of Independent States, and the Baltic States. World Health Organization. Publication WHO/Eur/NUT/98.1: 1-168.
- [20] Delong GR (1989) Observations on the neurology of endemic cretinism. In: Delong GR, Robbins J, Condliffe PG, eds. Iodine and the brain. New York, Plenum Press: 231ff.
- [21] Dobbing J & Sands J (1973) Quantitative growth and development of human brain. *Arch Dis Child* 48: 757-767.
- [22] Dunn, JT, Crutchfield HE, Gutekunst R, Dunn AD (1993) Methods for measuring iodine in urine. Wageningen: International Council for Control of Iodine Deficiency Disorders (ICCIDD) publ. 1-71.
- [23] Fenzi GF, Giusti LF, Aghini-Lombardi F, Bartalena L, Marcocci C, Santini F, Bargagna S, Brizzolara D, Ferretti G, Falciglia G (1990) Neuropsychological assessment in school-children from an area of moderate iodine deficiency. *J Endocrinol Invest* 13(5): 427-431.

- [24] Gerasimov G (2002) IDD in eastern Europe and central Asia. *IDD Newsletter* 18: 33-37.
- [25] Glinioer D (2001) Pregnancy and iodine. *Thyroid* 11 471-481.
- [26] Goldner T (2005) Tulburările prin deficit de iod - perspectiva națională - perspectiva regională (in Romanian) Second National Conference for the elimination of Iodine Deficiency Disorders, Bucharest, Bucharest, 14 November 2005.
- [27] Gorstein J (2001) Goiter assessment: help or hindrance in tracking progress in iodine deficiency disorders control program *Thyroid* 11: 1201-1202.
- [28] Gutekunst R & Teichert HM (1993) Requirements for goiter surveys and the determination of thyroid size. In: Delange F, Dunn JT, Glinioer D (eds.) Iodine deficiency in Europe. A continuing concern. Plenum Press, New York-London 109-115.
- [29] Gutekunst R & Scriba PC (1989) Goiter and iodine deficiency in Europe: the European Thyroid Association report as updated in 1988. *J Endocrinol Invest* 12: 209-220.
- [30] Hetzel BS (1983) Iodine deficiency disorders (IDD) and their eradication. *Lancet* 2: 1126-1129.
- [31] Hetzel BS, Dunn JT, Stanbury JB (1987) The prevention and control of iodine deficiency disorders. Elsevier 257.
- [32] Joffe RT & Sokolov ST (1994) Thyroid hormones, the brain, and affective disorders. *Crit Rev Neurobiol* 8: 45-63.
- [33] Koibuchi N & Chin WW (2000) Thyroid hormone action and brain development. *Trends Endocrinol Metab* 4: 123-128.
- [34] Kun I (2006) Insuficiența tirodiană în județul Mureș (in Romanian) Hypothyroidism in Mureș County Doctoral thesis, University of Medicine and Pharmacy Târgu Mureș, Romania.
- [35] Kun I, Szántó Zs, Kun IZ, Szabó B, Coroș L (2007) The evolution of hypothyroidism in pregnant women in County Mureș between 2001-2006. 9th European Congress of Endocrinology, 28 aprilie-2 mai 2007, Budapest, *Endocrine Abstracts* 14: P351.
- [36] Kun IZ, Szántó Zs (2003) A pajzsmirigyelégtelenség és szövődményeinek gyakorisága Maros megye területén (in Hungarian) The frequency and complications of hypothyroidism in Mureș County. In: Brassai A (ed.) *Orvostudományi Tanulmányok – Sapientia Könyvek*. Scientia Cluj-Napoca, pp. 131-206.
- [37] Laurberg P, Nohr SB, Pedersen KM, Hreidarsson AB, Andersen S, Bülow Pedersen I, Knudsen N, Perrild H, Jorgensen T, Ovesen L (2000) Thyroid disorders in mild iodine deficiency. *Thyroid* 10: 951-963.
- [38] Morreale de Escobar G, Obregon MJ, Escobar del Rey F (2004) Role of thyroid hormone during early brain development. *Eur J Endocrinol* 151 (Suppl. 3): U25-37.
- [39] Nanu M (2005) Evaluarea statusului iodului la femeia gravidă. Second National Conference for the elimination of Iodine Deficiency Disorders, Bucharest, 14 November 2005.

- [40] Neale DM, Cootauco AC, Burrow G (2007) Thyroid disease in pregnancy. *Clin Perinatol* 34: 543–557.
- [41] Pearce EN (2009) What do we know about iodine supplementation in pregnancy? *J Clin Endocrinol Metab* 94: 3188–3190.
- [42] Perez C, Scrimshaw S, Munoz A (1960) Technique of endemic goiter surveys. In *Endemic Goiter*, WHO Geneva, pp. 369–383.
- [43] Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Viljder JJ (2003) Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol* 59: 282–288.
- [44] Simescu M & Ionescu M (1998) Date despre IDD în România în contextul european actual. Considerații despre profilaxia iodată și monitorizarea ei. Hipotiroidismul tranzitoriu neonatal (in Romanian) *Revista de Medicină și Farmacie* 44(Suppl.3): 8–9.
- [45] Simescu M, Zbranca E, Dumitriu L (1999) Monitorizarea profilaxiei gușii endemice în județele în care Programul 21 se desfășoară (in Romanian) The Annual National Congress of Endocrinology, Constanța, Romania, Book of abstracts: 40.
- [46] Stanbury JB (1994) The damaged brain of iodine deficiency. New York, Cognizant Communication.
- [47] Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonqlet R, Vidor G, Baverman LE, Medeiros-Neto G (1998) Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* 8(1): 83–100.
- [48] Stănescu A (2005) Contextul nutrițional în România. Second National Conference for the elimination of Iodine Deficiency Disorders, Bucharest, 14 November 2005.
- [49] Szántó Zs, Kun I, Kun IZ, Coroș L, Cucerea M (2007) The influence of universal salt iodization on the iodine status reflected by TSH serum levels of newborns, in Mureș County, between years 2001–2006. *Acta Endocrinol (Buc)* III(3): 291–301.
- [50] Szybinski Z (2011) The WHO Recommendation on Reduction of Daily Salt Intake and its Impact on the USI Program for IDD Prevention. West Central Europe Regional ICCIDD Satellite to 35th Annual ETA Meeting. In: Paschke R & Smyth P (eds.) *Thyroid International* 5: 14.
- [51] Vasilescu Gh, Totoianu I, Ismănescu I (1986) Prevalence of endemic goiter in Mureș County. *Rev Roum Med Endocrinol* 24: 27–32.
- [52] Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F (1990) Defective neuromotor and cognitive ability in iodine deficient school-children of an endemic goiter region in Sicily. *J Clin Endocrinol Metab* 70: 379–384
- [53] Vermiglio F, Lo presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A, Artemisia A, Trimarchi F (2004) Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine

- deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 89: 6054-6060.
- [54] Vulpoi C, Mogoș V, Cojocaru M, Preda C, Ungureanu MC, Brănișteanu DD, Cristea C, Zbranca E (2002) Thyroid volume in a former iodine deficient area. *Revista Română de Endocrinologie și Metabolism* 1(3): 17-22.
- [55] Vitti P, Martino E, Anghini-Lombardi F, Rago T, Antonangeli L, Maccherini D, Nanni P, Loviselli A, Balestrieri A, Araneo G et al (1994) Thyroid volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. *J Clin Endocrinol Metab* 79(2): 600-603.
- [56] Witt P, Delange F, Pinchera A, Zimmermann M, Dunn JT (2003) Europe is iodine deficient. *Lancet* 5: 361.
- [57] Zbranca E, Găluscă B, Mogoș V (2008) Tiroida (in Romanian) In: Zbranca E (ed.): Endocrinologie. Ghid de diagnostic și tratament în bolile endocrine. Third edition. Polirom Iași 105-175.
- [58] Zimmermann MB, Molinari L, Spehl M, Weidinger-Toth J, Podoba J, Hess S, Delange F (2001) Toward a consensus on reference values for thyroid volume in iodine-replete school-children: results of a workshop on interobserver and inter-equipment variation in sonographic measurement of thyroid volume. *Eur J Endocrinol* 144: 213-220.
- [59] Zimmermann MB, Hess SY, Molinari L, de Benoist B, Delange F, Braverman LE, Fujieda K, Ito Y, Jooste PL, Moosa K, Pearce EN, Pretell EA, Shishiba Y (2004) New reference values for thyroid by ultrasound in iodine-sufficient school-children: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. *Am J Clinical Nutrition* 79: 231-237.
- [60] Zimmermann MB (2009) Iodine deficiency. *Endocr Rev* 30: 376.
- [61] ***Government of Romania (2005) National Strategy on the elimination of iodine deficiency disorders by universal iodization of salt intended for direct human use and for bread baking 2004-2012. UNICEF Romania Bucharest, 1-12.
- [62] ***WHO, UNICEF, ICCIDD (1994) Indicators for assessing iodine deficiency disorders and their control through salt iodization. WHO Geneva: WHO/NUT/94.6.
- [63] ***WHO, UNICEF, ICCIDD (1999) Progress towards the elimination of iodine deficiency disorders (IDD). WHO Geneva: WHO/NHD/99.4:1-33.
- [64] ***WHO, UNICEF, ICCIDD (2001) Assessment of iodine deficiency disorders and monitoring their elimination. WHO Geneva: WHO/NHD/01.1.