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History of Endemic Goiter in Croatia: From Severe Iodine Deficiency to Iodine Sufficiency

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A B S T R A C T

At the time after the Second World War, endemic goiter was present in most parts of Croatia with a prevalence of more than 50% and presence of cretinism. In the village of Rude near Zagreb, goiter was detected in 85% of school children with 2.3% of cretins in the village population. In 1953 the first regulation on obligatory salt iodination, requiring 10 mg of potassium iodide (KI) per kg of salt was established in former Yugoslavia. A three-fold reduction of goiter prevalence, together with disappearance of cretinism was recorded ten years later. In 1992, the National Committee for Eradication of Goiter was founded. The survey performed during 1991–1993 exhibited prevalence of goiter among school children between 8% and 35% and urinary iodine excretion under 10 μg/dL in most of the children from continental parts of the country. The new obligatory regulation, requiring 25 mg of KI/kg of salt, was proposed by the National Comittee and finally established in 1996. In 2002 thyroid volumes and medians of urinary iodine excretion were normal according to the ICCIDD criteria. Overall median of urinary iodine excretion for schoolchildren in Croatia was 14 ug/dL. Croatia crossed a path from severe iodine deficiency detected in the 1950', to the period of mild to moderate iodine deficiency during the 1990', and finally, nowadays, iodine sufficiency has been achieved.

***Key words**: iodine deficiency disorders (IDD), endemic goiter, prevention, salt iodination, IDD status, Croatia, urinary iodine excretion, thyroid volume, schoolchildren*

Introduction

The history of goiter and cretinism

The first records of goiter and cretinism date back to ancient civilizations including the Chinese and Hindu cultures and also Greek and Roman. One of the oldest references to goiter is attributed to the legendary Chinese Emperor Shen-Nung (2838–2698 BC) who, in his book *Pen-Ts'ao-Tsing* (*A treatise on herbs and roots*) is said to have mentioned the seaweed Sargasso as an effective remedy for goiter. The Chinese even used animal thyroid in the treatment of goiter.

The oldest known representation of goiter is in the Buddha frieze of Gandhara, now in Pakistan (2nd/3rd C AD). Among numerous figures, is a man with a large goiter. His facial expression suggests idiocy. Several Roman authors wrote on the prevalence of goiter in the Alps. The »father of medicine«, Hippocrates, regarded poor drinking water as a cause of goiter. The great physician Galen (AD 132–200) concluded that the glands of the neck, including the thyroid had the function of secreting a fluid into the larynx and the pharynx. In the Middle Ages goitrous cretins usually appeared in pictoral art, often as angels or demons. During the Renaissance, the paintings of the Madonna in Italy so commonly showed goiter that the condition must have been regarded as normal.

The function of the thyroid was not understood until the latter part of the 19th century when it was recognized to have an »internal« secretion in the form of the thyroid hormone, and not an external one. The iodination of salt was first suggested by Boussingault, who lived for many years in Colombia, South America, and discovered that the local people benefit from salt obtained from an abandoned mine in Guaca, Antioquia. In 1825 Boussingault analyzed this salt and found large quantities of iodine. Subsequently, in 1833 he suggested that iodized salt be used for the prevention of goiter. Present-day practice in the prevention and control of goiter is based on the work of David Marine who carried out the first large-scale trials with iodine over the pe-

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riod 1916–20 in Akron, Ohio, USA. In 1922 Switzerland introduced mass iodine prophylaxis. Following the introduction of iodized salt, goiter incidence fell steeply. Later, deaf and dumb institutions were closed. In 1924 iodination of salt was introduced in Austria, Bavaria and USA[1].

Basic physiological and epidemiological notions

Iodine is an essential element for normal growth and development in animals and men. It occurs in the human body in minute amounts (15–20 mg). The special biological importance of iodine arises from the fact that it is a constituent of thyroid hormones. The essential requirement for normal growth is only 100–150 μg/day[2]), but the optimal intake for adult is about 200–300 μg daily[3]. The principal source of iodine for human consumption is food. The highest iodine content is found in fish and, to a lesser extent, in milk, eggs and meat. Very low iodine content is usually found in fruits, vegetables and drinking water[3].

The reduction of iodine intake in the organism below a specific minimum causes a number of functional and developmental abnormalities, including thyroid function abnormalities and, when iodine deficiency is severe, endemic goiter and cretinism[4]. In 1983 Hetzel introduced the notion iodine deficiency disorders (IDD)[5] and, in addition to goiter and cretinism, drew attention to other disorders caused by iodine deficiency, especially brain damage. According to Hetzel[5], the spectrum of iodine deficiency disorders comprise goiter, stillbirths and miscarriages, increased perinatal mortality, reduced fertility, neonatal and juvenile thyroid deficiency, dwarfism, mental defects, deaf mutism, spastic weakness and paralysis, as well as lesser degrees of loss of physical and mental function. By definition all these conditions can be prevented by correction of iodine deficiency.

Regarding the severity of IDD, three different degrees have been considered: mild, moderate and severe[3]. Mild to moderate iodine deficiency is typically seen in Europe, while severe iodine deficiency is present in the developing countries of the Third World. Endemic cretinism is the most important complication of severe iodine deficiency and therefore, the most important public health problem. It is characterized by irreversible brain damage and mental retardation, which result from iodine deficiency and thyroid failure during fetal and early postnatal life. It is believed that about 20 million people all over the world are significantly mentally handicapped as a consequence of iodine deficiency[6]. Based on the most recent evaluation between 40 and 50 million newborns a year remain unprotected from mental retardation caused by iodine deficiency[7].

There is a cycle of iodine in nature. Most iodine resides in the ocean. The large amounts of iodine were leached from the surface soil by glaciations, snow and rain, carried by wind, rivers and floods into the see. Therefore, the most likely areas to be leached are mountainous areas. The most severely deficient areas of the world are Himalayas, the Andes, the European Alps and the mountains of China[2], but the iodine deficient areas are also lowlands far from the oceans, such as in central parts of Africa, and to a lesser extent, lowlands of Europe[3].

At the beginning of the 1990's, IDD represented a significant public health problem for about 1570 million people in 110 countries (29% of the world population) and about 660 million were affected by goiter[3]. Iodine deficiency is a major public health problem in developing countries. Epidemiological studies carried out in the African villages demonstrated overall goiter prevalence from 50 to 85%[8,10] and presence of cretinism close to 1–1,5% of the village population[9,11].

Endemic goiter exists in a certain area if 5% of the children from 6–12 years of age have enlarged thyroid gland[12]. Iodine deficiency is the most significant etiological factor of endemic goiter[3,4,6,13]. The pituitary gland responds to low levels of circulating thyroid hormones by increasing secretion of thyroid stimulating hormone (TSH) and causing goiter as compensatory adaptation to iodine deficiency. In severe endemic areas the disease appears very early in the life with sharply increasing prevalence in both boys and girls and attains a peak value during puberty and childbearing age. From the age of 10, the prevalence is higher in girls than in boys. During adulthood the prevalence of goiter is decreasing in both sexes, but the decline is sharper in men than in women[3]. A higher prevalence of goitre is found in children of goitrous parents than in those of normal parents. However, the genetic factors have not been extensively analysed in endemic goiter[14]. The persistence of goiter despite sufficient iodine intake may suggest the presence of naturally occurring goitrogenic factors in the diet. Cassava is the basic diet in several African countries with endemic goiter[14,15]. Thiocyanate is liberated during the processing of cassava and this anion blocks the uptake of iodide by the thyroid.

Prevention and control of iodine deficiency disorders

Prevention and control of IDD can be easily achieved by appropriate iodine supplementation. Iodized salt, iodized oil, iodized bread, and iodized water can be used. Salt iodination is most frequently used for iodine prophylaxis, mainly in the form of potassium iodide (KI), but iodate (KIO3) is preferred in humid tropical regions, owing to its greater stability[16]. The recommended levels of iodine supplementation vary in different countries from the amounts of 10 to even 100 mg/kg of salt[3]. There were some attempts to iodinate bread (Holland and Tasmania), but the method was rejected. Iodination of irrigation water has been successfully used in China. In many developing countries with severe iodine deficiency, programs of iodine prophylaxis failed to prevent or eradicate IDD. The most often, iodized salt didn't reach the endemic areas or other socioeconomic, climatic, or geographic conditions limited the effectiveness of the programs. Administration of large quantities of iodine in the form of slowly resorbable iodized oil, given by intramuscular injections or orally, showed to be extremely effective in such conditions, especially in isolated communities[16–18].

Salt iodination sometimes causes hyperthyroidism. This complication was first noticed in the early days of iodine prophylaxis, especially in the old age group and was attributed to the presence of autonomous nodules or underlying Graves disease[3]. During the past decade a great progress was made worldwide in consumption of iodized salt. Today, close to 70% of the world's population uses iodised salt[7].

Epidemiological investigations of goiter in a certain area as a rule include schoolchildren and youth, since they reflect the current status in the population, while goiter in adults could be the consequence of iodine deficiency in the past. Inspection and palpation are most frequently used methods during an examination but the most precise measurement of the thyroid volume can be performed by ultrasound (USG). Due to technical reasons, it can be performed only for a limited number of subjects. The USG results need to be compared with normative values for USG thyroid volume in iodine sufficiency, and these values must be established for each population group. The upper limit of normal is taken as the volume at the 97th percentile of the corresponding iodine sufficient group[12].

Iodine intake in the organism is most precisely estimated by measurement of urinary iodine excretion, where the results of less than 50 μg in 24 hours indicate inadequate iodine intake. Urinary iodine excretion is the most useful impact indicator of severity of iodine deficiency. A median value equal or above 10 μg/dL declares normal iodine nutrition in the population. While a median of 10 μg/dL would imply that 50% of the samples are below 10 μg/dL, care must be taken to ensure that values below 5 μg/dL are limited to less than 20%[12]. Primary TSH screening for congenital hypothyroidism in newborns is a particularly sensitive index in the evaluation of iodine deficiency. In conditions of adequate iodine intake the frequency of neonatal TSH above 5 mU/L should be below 3%. A frequency between 3% and 19,9% would indicate mild IDD. A frequency between 20% and 39,9% would indicate moderate IDD, and frequency above 80% suggests severe IDD. Elevated serum TSH in the neonate indicates insufficient supply of thyroid hormones to the developing brain[19]. In addition, to declare the sustainable elimination of iodine deficiency as a public health problem the proportion of households consuming effectively iodised salt have to be more than 90%[12]. The impact indicators and severity of iodine deficiency are presented in Table 1.

The protocol on IDD investigation in a certain region must comprise geology, climate, ethnic group and alimentation. It is necessary to choose the village of reference with a population of more than 1000 individuals. The investigation have to include goiter, nodule and cretinism prevalence, biological and genetic traits, as well as toxicology (thiocyanates), nutrition and eradication[17].

The History of Endemic Goiter in Croatia

Endemic goiter was first recorded in Croatia since medieval times. One of the first scientific facts concerning goiter can be found in reports by the Austro-Hungarian army (1870–1882) about recruits with thick necks who were shorter than 154.5 cm[20]. Modern epidemiological investigations on goiter in Croatia, as part of former Yugoslavia, began after the Second World War. In the early 1950's it was estimated that 2 million people in the former Yugoslavia had goiter, with varying frequency ranging from 10 to 90 %. The endemic areas were inhabited by 6 million people who were considered a high-risk group, with approximately 20,000 cases of endemic cretinism and from 2,000 to 4,000 deaf-mute persons. The ratio of male and female children in many areas with goiter was 1:1, which indicated the severity of the situation. A large number of people in the epicenters of goiter were short in height and/or with low intelligence[21]. At the same time, the incidence of goiter was also high in neighboring countries.

In 1953 Josip Matovinović published the first map of goiter distribution in the former Yugoslavia[21]. Iodine deficiency disorders in Croatia appeared mostly in isolated northern and northeastern areas of the Sava and Drava river basins, as well as in mountainous regions of the northwest. The Adriatic coast seemed to have been the only part of the country where endemic goiter did not appear as a public health problem. The epidemiological investigations from this period demonstrated that iodine deficiency was the main etiological factor of endemic goiter. The incidence of goiter of over 40% on the island of Krk was attributed to strumogenous substances[22,23]. In the early 1950's the incidence of goiter in the continental parts of Croatia was: Osijek 83%, Požega 75%, Bjelovar 51%, Varaždin 71%, Sisak 88%, and Kordun 62%[20]. High incidence of goiter was also determined in Zagreb (Figure 1)[24].

In the village of Rude, near Zagreb, goiter was detected in 85% of children (Figure 2) with 2.3% of cretins in the village population[25]. The girls from this village were not considered pretty if they had »no neck« and even angels in the village church, near the village of

TABLE 1
IMPACT INDICATORS AND SEVERITY OF IODINE DEFICIENCY

Indicator	None	Mild	Moderate	Severe
Median urinary iodine concentration (μg/dL)	> 10.0	5.0–9.9	2.0–4.9	<2.0
Goiter prevalence	<5%	5.0–19.9%	20–29.9%	>30%

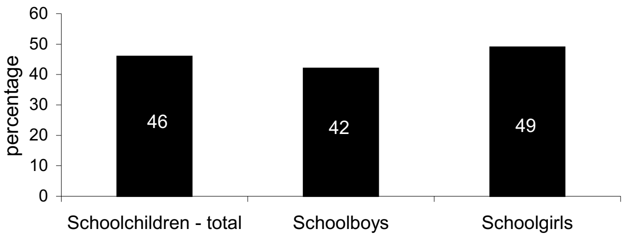

Fig. 1. The prevalence of goiter in Zagreb, 1953–1954. (Prebeg et al.)

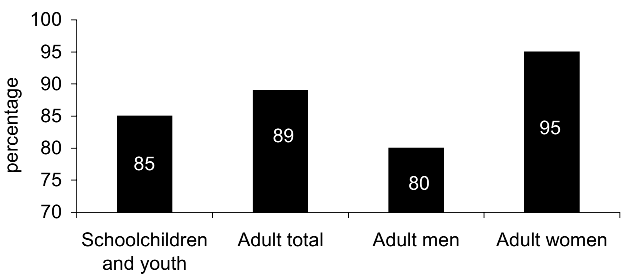

Fig. 2. The prevalence of goiter in the village of Rude, 1952. (Ferber et al.)

Rude, were represented with a goiter (Figure 3)**.** The research by Forenbacher and his colleagues[26–28] indicated that iodine deficiency and goiter were also significant in domestic animals due to frequent incidence of infertility, reduced production of milk and perinatal death of bovine (Table 2)[28]. This caused significant economic damage. Between 1930 and 1941 iodine prophylaxis began in former Yugoslavia with the distribution of iodized salt in some areas with severe incidence of endemic goiter. This practice was continued after the Second World War, but these measures proved to be insufficient, mostly because the population from the endemic areas acquired cheap non-iodized salt from the neighboring non-endemic areas. After many discussions, it was concluded that regional prophylaxis is not appropriate due to the severity of the illness and scattered distribution of endemic areas[20].

Fig. 3. Angel with goiter, in the village church near the vilage of Rude, where 85% of the children had goiter in 1950's.

TABLE 2
THE GOITER AMONG COWS, DISTRICT KOPRIVNICA, 1963. (FORENBACHER et al.)

Age (years)	Goiter %
0–1	24.9
1–5	37.5
5–10	54.0
10–15	64.4
>15	66.7

The first law on obligatory salt iodination in former Yugoslavia

The legal regulation on obligatory salt iodination for human and animal consumption requiring 10 mg of KI/kg of salt (with permitted oscillation of 5 mg/kg) was reached in 1953. At the time, it was one of the most progressive laws on salt iodination in Europe. The program was implemented gradually over a years. Until 1954 salt was iodized with 5 mg and afterwards with 10 mg of iodine. The average iodine intake was estimated in the range of 76 to 114 μg/day[29]. A temporary increase in incidence of autoimmune and non-autoimmune thyrotoxicosis was recorded only at the beginning of iodine prophylaxis. Iodination of salt for animal consumption has begun in 1957 on a large scale[20].

Ten years later a three-fold reduction of goiter prevalence, together with disappearance of cretinism, was recorded in all endangered areas of the country (Figure 4)[30]. However, the goiter was still found in 20–30% of children. In the endemic areas the structure of growth normalized and there was an increase of intellectual abilities and success in school among children. Many researches indicated a decrease of iodine accumulation in the thyroid gland.

Subsequently there was a rather long period without any significant research in this area. It was considered

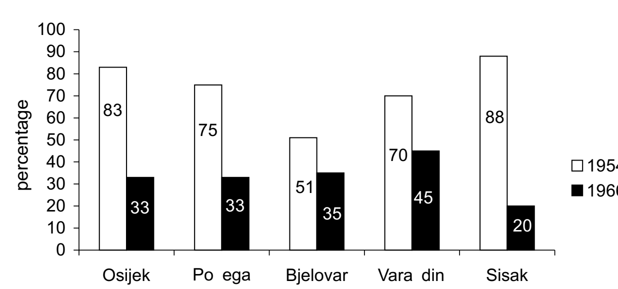

Fig. 4. The incidence of goiter among children before salt iodination (1954), and after ten years of salt iodination (1966).

that iodine deficiency disorders were mostly eradicated and no longer existed as a public health problem in Croatia. There were no significant differences in the concentration of T3, T4 and TSH among subjects with and without goiter[31,32].

Nevertheless, some research of urinary iodine excretion, in relation to the creatinin, indicated a borderline low iodine intake within subjects in Zagreb[33]. A relatively high incidence of goiter among schoolchildren, high incidence of toxic thyroid adenomas and increased 131-I uptake test in euthyroid subjects indicated that problem of iodine deficiency in Croatia still existed[34–36].

The National Committee for Eradication of Goiter and Control of Iodine Prophylaxis

In 1992, the Minister of Health Andrija Hebrang founded ''The National Committee for Eradication of Goiter and Control of Iodine Prophylaxis''. According to a recommendation by ICCIDD, experts of various backgrounds were appointed in the Committee: Zvonko Kusić was appointed chairman and the following were members: Head of the Department of Sanitary Inspection at the Ministry of Health, a legal assistant at the Ministry of Health, a representative of Croatian National Institute of Public Health, a representative of the Veterinary Faculty and a director of the largest salt plant in Croatia. The structure of the Committee, consisting of the experts of various backgrounds, ensured a multidisciplinary approach to the problem. Herewith Croatia was included in an action of the WHO and UNICEF with the goal of eradicating iodine deficiency disorders by the year 2000[20]. The Committee initiated a comprehensive epidemiological research with the aim of determining the state of iodine intake in different parts of Croatia.

The nationwide survey during 1991–1993.

The survey was carried out in four major Croatian regions, under the leadership of Department of Nuclear medicine »Sisters of Charity« University Hospital, Zagreb. Due to the epidemiological reasons, connected with possible different living and eating habits, investigation included randomly selected schoolchildren from regional centers and neighboring smaller towns and villages of northwestern Croatia, Slavonia, nothern Adriatic and Dalmatia. A total of 2436 schoolchildren of both sexes, aged 7–15 years were included in the study. According to the age, the children were divided into two major groups: younger one, 7–11 years, and older one, 12–15 years. The prevalence of goiter among schoolchildren was determined by palpation of the neck according to the PAHO/WHO classification[37]. The children from Zagreb were examined by ultrasound of the thyroid gland. Urinary iodine excretion was measured by the instructions of ICCIDD/WHO and modified colometric method based on the Sandell-Kalthoff reaction[38]. The content of iodine in salt samples was determined by the original titrimetric method ESPA/CN 1097 CX[39].

The results of the investigation demonstrated that mild to moderate iodine deficiency still persisted in Croatia[40–42]. Total prevalence of goiter among schoolchildren ranged from 8% to 35% (Figure 5 and 6). In Zagreb, 5–13.2% of schoolchildren had thyroid volume measured by ultrasound above the upper limit for their age, according to the reference values (Figure 7). These results were similar to those measured in the corre-

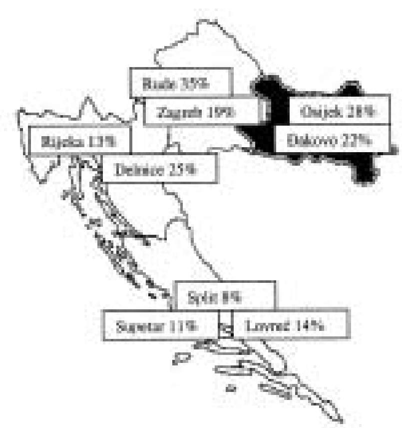

Fig. 5. Total incidence of goiter in schoolchildren determined by palpation, 1991–1993.

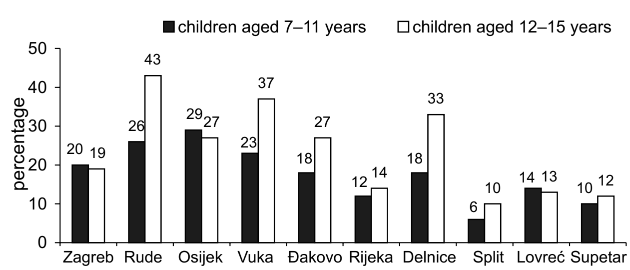

Fig. 6. The incidence of goiter determined by palpation, 1991–1993.

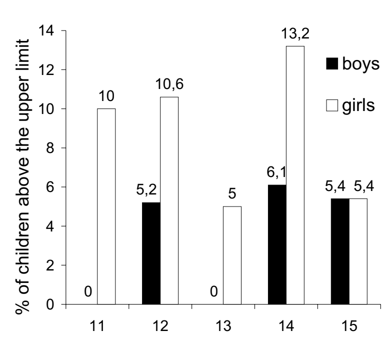

Fig. 7. Thyroid volume in schoolchildren from Zagreb determined by ultrasound, 1991.

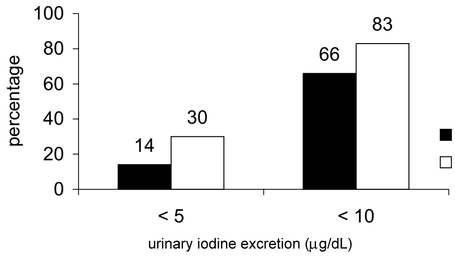

Fig. 8. Urinary iodine excretion in schoolchildren from Zagreb and Rude, 1991.

sponding age group in southern Germany (9mL) and almost double the size of thyroid volume of children in Sweden (4 mL)[20]. In continental parts of Croatia (Zagreb and Rude), 14–30% of schoolchildren had urinary iodine excretion below 5 µg/dL, and 66–83% below 10 µg/dL. (Figure 8). Control of salt produced in the Croatian largest salt plant Pag revealed an average KI value of 8,3 mg/kg[40–42].

A systematic research of epidemiology of goiter was implemented on the island of Krk. It confirmed a rather high prevalence of goiter among schoolchildren (29%), regardless of apparently similar conditions on the island of Cres (6.7%). It suggests the presence of other etiological factors, mostly nutritional goitrogenes on the island of Krk[20].

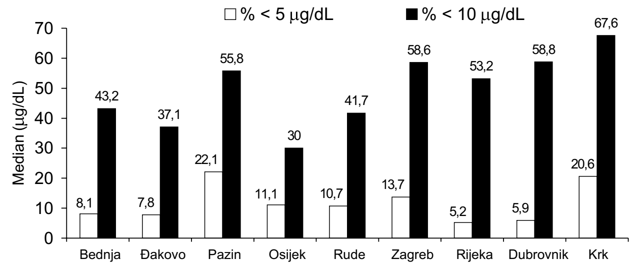

Fig. 9. Urinary iodine excretion in schoolchildren (n=765), 1997.

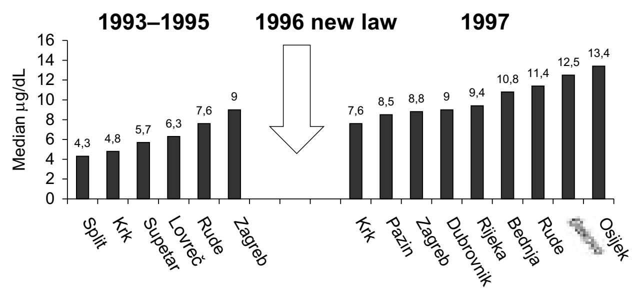

Fig. 10. Median of urinary iodine excretion in schoolchildren aged 7–15 years before (1993–1995) and a year after the new regulation on obligatory salt iodination (1997).

The new Croatian Regulation on Obligatory Salt Iodination

The new obligatory regulation[43–45], requiring 25 mg of KI/kg of salt was proposed by the Committee in the year 1996 and soon thereafter issued by the Minister of Health. Concurrently with the change of regulation, a national program for monitoring of iodine prophylaxis was established with the main goals:

1) Control of iodine in salt at all levels, from producers to consumers

2) Control of IDD with regular epidemiological research of thyroid size, urinary iodine excretion in randomly selected schoolchildren population, and control of neonatal TSH

3) Control of iodine induced hyperthyroidism

The first epidemiological studies after the new regulation

The first survey was performed in 1997. A total of 663 schoolchildren of both sexes, aged 9 to 16 years, from four major geographical regions of Croatia were included in the survey. The first positive results of improved iodine intake, obtained by measurement of urinary iodine excretion, were detected[46]. Measurement of urinary iodine excretion ill all parts of Croatia revealed that 5.2–22.1% of schoolchildren had less than 5 µg/dL and 30–58.6% less than 10 µg/dL (Figure 9). The medians of urinary iodine excretion were slightly higher (7.6–13.4 µg/dL) than those obtained prior to the introduction of a new regulation (4.3–9 µg/dL) (Figure 10). These medians corresponded to the values in Austria (9.8–12 µg/dL) or Slovakia (13–14.3 µg/dL) and were higher than values in the Czeck Republic (8.5–8.7 µg/dL), and more homogenous than values in Hungary (5.2–11.5 µg/dL)[12]. In Rude, in 10.7% of schoolchildren urinary iodine excretion was less than 5 µg/dL, and in 41.7% less than 10 µg/dL. Thyroid volume in schoolchildren from Zagreb and Rude in 1999 was within the normal range according to the ICCIDD criteria. Less than 20 mg of KI/kg of salt were found in 14% of salt samples taken from hausholds in 1999. The salt produced in Croatian salt plants in Pag and Nin was completely in agreement with the new regulation[46].

Croatia has Reached Iodine Sufficiency

In 2002 Croatia has finally reached iodine sufficiency[47–49]. A total of 927 schoolchildren of both sexes, aged 6–12 years were included in the survey. Thyroid volumes of school children from all four major Croatian regions were for the first time within the normal range according to the provisional WHO/ICCIDD reference values[50] in iodine-replete school-age children, updated in 2001. The medians of urinary iodine excretion, detected in all four regions, were within the normal range according to the ICCIDD criteria; 14.6 ug/dL in Zagreb, 13.1

ug/dL in Split, 14.2 ug/dL in Rijeka, and 14.7 ug/dL in Osijek. The medians were higher in comparison to the medians in 1990', before the new regulation (from 4.3 to 9 ug/dL) (Figure 11). An overall median of 14.0 ug/dL of urinary iodine excretion was detected for all target areas. Both domestic and imported salt corresponded with the effective regulation on iodination. TSH measurements in newborns, performed in 2001, showed that 5,2% were above 5 mU/L[47,48].

Croatia crossed a path from severe iodine deficiency detected in the 1950', to the period of mild to moderate iodine deficiency during the 1990', and finally, nowadays, iodine sufficiency has been achieved.

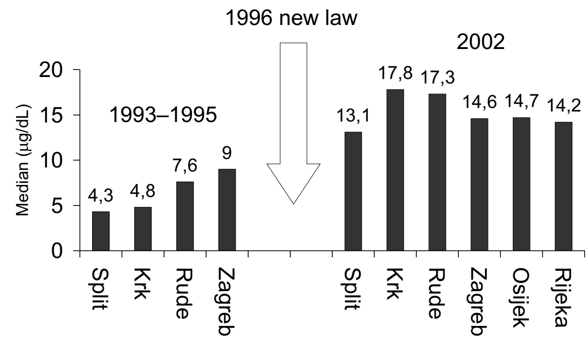

Fig. 11. Medians of urinary iodine excretion (µg/dL) before the new regulation on obligatory salt iodination (1993–1995) in comparison to medians in 2002.

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POVIJEST GUŠAVOSTI U HRVATSKOJ: OD TEŠKOG NEDOSTATKA JODA DO DOSTATNOSTI

S A Ž E T A K

U doba nakon Drugog svjetskog rata, endemska gušavost bila je prisutna u većem dijelu Hrvatske s prevalencijom od preko 50% i pojavom kretenizma. U selu Rude kraj Zagreba gušavost je detektirana u 85% školske djece s 2,3% kretena u selu. Tijekom 1953. uvedeno je obvezno jodiranje soli, s 10 mg kalij jodidi na kilogram soli. Deset godina kasnije detektirana je trostruka redukcija gušavosti i nestanak kretenizma. Tijekom 1992 oformljen je Državni odbor za eradikaciju gušavosti. Studija provedena tijekom 1991.–1993. pokazala je učestalost gušavosti između 8% i 35% među školskom djecom, uz urinarnu ekskreciju joda manju od 10 μg/dL u kontinentalnom dijelu Hrvatske. Nova pravila koja zahtjevaju 25 mg KI/kg soli uvedena su 1996. Tijekom 2002. tiroidni volumeni i medijani urinarne ekskrecije bili su normalni u skladu s ICCIDD kriterijima. Medijan urinarne ekskrecije za školsku djecu bio je 14 ug/dL. Hrvatska je prošla put od teškog nedostatka joda u 50-ima, do perioda umjerenog manjka u 90-ima, i konačno do današnje dostatnosti joda.