Review

IODINE DEFICIENCY IN LATVIA: CURRENT STATUS AND NEED FOR NATIONAL RECOMMENDATIONS

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In the absence of a mandatory salt iodisation programme, two nationwide cross-sectional cluster surveys revealed persisting iodine deficiency among Latvian schoolchildren during the spring season and a noteworthy iodine deficiency in pregnant women in Latvia; these deficiencies warrant intervention. The consequences of mild-to-moderate iodine deficiency during pregnancy and lactation can adversely affect foetal brain development. Data from a Latvian population survey revealed the consumption of approximately 100 µg of iodine per day through foods and iodised salt. Therefore, strategies to increase the consumption of iodine-containing products should be implemented, particularly for children. In addition, to meet the increased iodine requirement during pregnancy, pregnant women should take daily supplements containing 150 µg iodine from the earliest time possible. All women of childbearing age should be advised to increase their dietary iodine intake by using iodised table salt and iodine-rich products: seafood, milk and milk products. For women with pre-existing thyroid pathologies, the medical decision should be considered on a case-by-case basis. Urinary iodine concentration monitoring among schoolchildren and pregnant women and neonatal thyrotropin registry analysis every five years would be an appropriate strategy for maintaining iodine intake within the interval that prevents iodine deficiency disorders.

Key words: *iodine deficiency, children, pregnancy, iodine supplementation.*

INTRODUCTION

Iodine is an essential micronutrient that is required for adequate thyroid hormone production. In adults, mild-to-moderate iodine deficiency appears to be associated with higher rates of the more aggressive subtypes of thyroid cancer and increased risk of diffuse goitre with the associated hypothyroidism, nontoxic goitre and toxic nodular goitre (Anonymous, 2008). Sufficient iodine intake is extremely important during pregnancy, breastfeeding and early childhood because even a mild iodine deficiency has the potential to impair optimal brain development (Pearce *et al.,* 2013; Gowachirapant *et al.,* 2009). According to the World Health Organisation (WHO) guidelines, the median urinary iodine concentration (UIC) in iodine-sufficient populations should be greater than 100 µg/g Cr, and less than 20% of the popu-

lation can have a UIC below 50 µg/g Cr (Bernal and Nunez, 1995). Accordingly, mild iodine deficiency is defined as a urinary iodine excretion of 50–99 µg/g Cr, moderate deficiency as 20–49 µg/g Cr, and severe deficiency as less than 20 µg/g Cr (Ausó *et al.,* 2004). Although the prevalence of iodine deficiency in Europe has decreased by almost 30% over the past decade, it still remains the leading cause of preventable intellectual impairment (Gowachirapant *et al.,* 2009; Pearce *et al.,* 2013) and is the primary motivation behind the current worldwide drive to eliminate iodine deficiency. The term iodine deficiency disorders (IDD) is used to define a group of diseases resulting from a relative loss of iodine in the diet, including those from multiple defects, which may be prevented by ensuring adequate intake (Anonymous, 2008; Huang *et al.,* 2013). Despite good health indicators in the European Union, IDD prevention

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programmes have not been universally introduced, and parts of Europe have poor or incomplete access to iodised salt (Delange, 2002).

High-quality population data on iodine intake are required to assess the population status and to design strategies to correct deficiencies without introducing excessive intake. During the last five years, two nationwide cross-sectional cluster surveys on iodine nutrition have been performed in Latvia (Konrade *et al.,* 2012; 2015; 2014); these data serve as the basis for national recommendations.

IODINE SOURCES

Iodine is obtained from the diet and is primarily absorbed by the gastrointestinal tract in the inorganic anionic form of iodide. Several studies have suggested that proximity to the sea and seaweed abundance are factors that support an adequate iodine supply, because seawater has the highest iodine concentration of nearly 58 µg/L (Pessah-Pollack *et al.*, 2014). Because the Baltic Sea coast of Latvia extends for more than 500 kilometres, iodine is a largely overlooked nutrient in the country. The iodine cycling from seawater in many regions is slow and incomplete; thus, soils and drinking water are depleted of iodine, and populations in coastal regions can also be iodine deficient (Bath *et al.*, 2013). In addition, foods of marine origin having the highest iodine concentration are not widely used in everyday meals in Latvia (Grīnberga *et al.*, 2015). Most other foods and beverages have low iodine content (Table 1); thus, iodine fortification of table and industrial salt is the most convenient option. The advantage of iodised salt is that it is used by nearly all of society, irrespective of social and economic status.

According to the results of salt consumption analysis in 1999, less than 1% of all edible salt in Latvia was iodised (Selga *et al.*, 2000); however, in 2014, the FinBalt study found an approximately 10-fold increase: 6.9% of men and 9.4% of women reported an intake of iodised salt (Grīnberga *et al.*, 2015). In 2010–2011, the self-reported prevalence of regular iodised salt consumption by Latvian schoolchildren was similar, i.e., 10.2% (Konrade *et al.*, 2014).

Current efforts aimed at preventing iodine deficiency not only stipulate iodisation of all household table salts but also include other alternatives to increase the consumption of iodine-rich marine and additional iodine-fortified products (e.g., milk, mineral water) with standardised levels of iodine (Moleti *et al.*, 2011). In several countries, cow milk is considered an important source of dietary iodine (Konrade *et al.*, 2012), and associations between low urinary iodine excretion and a low intake of milk have been reported (Becker *et al.*, 2006).

Foods such as milk and bread are sources of iodine due to the iodine-containing compounds used in agriculture and the use of iodised salt in food preparation (Speeckaert *et al.*, 2011). In some countries, including the USA and Switzerland, the use of iodine-containing disinfectants or food supplements in cow fodder are determined by local regulations. However, no such regulations exist in Latvia. Consequently, statistical data are not routinely collected. We conducted a short survey of local farmers. We enrolled 37 farmers; 10 reported using iodophors, and 28 used iodine- fortified fodder. The median iodine content in the analysed samples was 546.9 (IQR 311.9; 759.2) µg/L (Neimane, unpublished data). There was wide variation of iodine concentration ranging from 212.6 to 1298.7 µg/L. Milk samples were collected in both winter and summer, and the iodine content was similar among seasons. The fat content of milk did not correlate significantly with iodine concentration. However, a larger sample size would be necessary to verify these results. Nevertheless, our recent study showed that the median UIC was significantly lower in women who reported only rare milk product consumption than in women who consumed approximately three servings of milk products daily (Konrade *et al.,* 2015).

Dietary supplements are a significant source of iodine, especially during pregnancy. Our studies revealed that less than 20% of pregnant women reported the use of iodine-containing supplements, and only 6.8 % used supplements with an iodine content of ≥ 150 µg; this supplementation resulted in a slightly higher median UIC compared with those of the group of women who did not use iodine-containing supplements and those who used supplements with an iodine content of < 100 µg (Konrade *et al.,* 2015). These findings indicate that iodine-containing supplements, dairy products and iodised salt are the most important iodine sources in Latvia.

IMPORTANCE OF ADEQUATE IODINE NUTRITION

Iodine deficiency occurs when the iodine intake does not meet the recommended levels. The term IDD is used to describe the consequences of iodine deficiency in a popula-

Table 1

IODINE CONTENT IN 100 GRAMS OF FOOD (Dahl *et al.*, 2009)

Food	Iodine (µg/100 g)
Iodized salt	2000
Cod, baked	130
Lobster, boiled	130
Caviar	117
Sardine, in tomato sauce, canned	67
Salmon, farmed, raw	44
Shrimp or prawn, cooked	37
Egg	39
Milk*	15–37
Yoghurt*	18–24
Cheese (45%, Edam, Cheddar)	13–75
Potatoes	2
Fruits and berries	2

* Content may vary according to the geographical area and the iodine content of the soil

tion; this deficiency may be prevented by ensuring adequate iodine intake (Anonymous, 2008; Rohner *et al.*, 2014). In the adult population, iodine deficiency is associated with an increased rate of goiter, hyperfunctioning thyroid nodules, hypothyroidism, and diminished working ability and productivity. Regardless of age, there is also a latent risk of increased thyroid susceptibility to nuclear radiation. IDD is associated with a higher incidence rate of thyroid cancer and with an altered ratio of papillary to follicular neoplasia. In the state of iodine sufficiency, a significant predominance of papillary carcinoma is observed. This alteration means that, in fact, thyroid cancer subtypes shift towards more malignant forms (de Benoist *et al.*, 2009).

However, the most significant effects result from insufficient iodine levels during pregnancy and the immediate postpartum period. A meta-analysis published in 2013 revealed that at age 5, children lost 7.4 IQ points due to iodine deficiency during pregnancy (Bougma *et al.*, 2013). Econometric models have established that this result not only is significant at the individual level but also affects society as a whole: a one-point decrease in IQ has been associated with a persistent 0.11% annual decrease in per capita gross domestic product (GDP). This effect is connected with an economic recession and translates into a decrease in productivity (Jones and Schneider, 2006). These substantial consequences result from even mild iodine deficiency, which disrupts the metabolism of thyroid hormones — a critical endocrine regulator of early brain development (Bernal and Nunez, 1995). The thyroid hormone regulates a specific gene underlying major neurodevelopmental events. This effect plays a significant role in neurogenesis, axon and dendrite formation, neuronal migration, synaptogenesis and myelination (Berbel *et al.*, 1985; Berbel *et al.*, 1994; Morreale De Escobar *et al.*, 2000; Ausó *et al.*, 2004; Cuevas *et al.*, 2005). Furthermore, thyroid hormones are a key regulator of the basal metabolic rate and macronutrient metabolism (Oppenheimer *et al.*, 1987).

IODINE STATUS IN CHILDREN

The first nationwide cross-sectional school-based cluster survey of IDD in Latvia was performed in 2000, when 587 schoolchildren were tested. The survey revealed a median UIC of 59 µg/L, which was indicative of a mild iodine deficiency; severe iodine deficiency was observed in 19.2% (n = 115) of the participants (Selga *et al.*, 2000). Additionally, the Latvian neonatal thyrotropin (TSH) screening data from 2000–2002 provided evidence that Latvia is an iodine-deficient region (Gyurjyan *et al.*, 2006).

A 10-year follow-up cross-sectional interseasonal school-based cluster survey was performed in October 2010 and April 2011 (Fig. 1). In addition, as a tool to monitor iodine deficiency during pregnancy, the Latvian Neonatal TSH screening data (prevalence of TSH 5 mIU/L) from 31,274 newborns in 2009–2010 were analysed. The UIC was found to be at the lower end of the normal range (107.3 µg/g) (Konrade *et al.*, 2014), which can be considered an im-
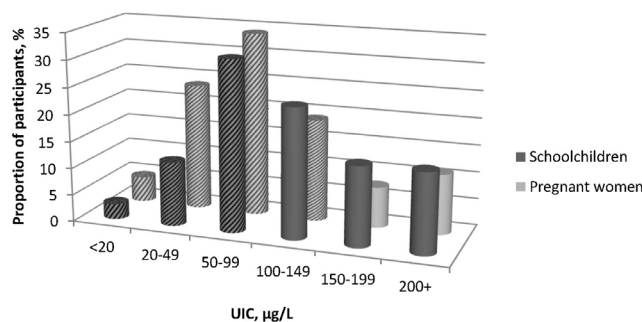

Fig. 1. Urinary iodine concentration (UIC) in Latvian schoolchildren (dark grey) and pregnant women (light grey). The striped columns represent UIC values below the normal range of the respective population, and the solid coloured columns are within the normal range. Cluster survey of schoolchildren performed in October 2010 and April 2011 (Konrade *et al.*, 2014), and national survey of pregnant women carried out during the spring and autumn seasons in 2013 (Konrade *et al.*, 2015).

provement compared with results of the previous nationwide cross-sectional school study (Selga *et al.*, 2000). Similar to the results of other studies conducted in mild iodine-deficient regions of Europe (Als *et al.*, 2003; Moreno-Reyes *et al.*, 2011; Arrizabalaga *et al.*, 2012), we found seasonal UIC fluctuations. In autumn, the UIC was at the lower end of the normal range (129.7 µg/g Cr), but it was significantly lower during the spring sampling (78.3 µg/g Cr) (Konrade *et al.*, 2014). Interestingly, our study results showed fluctuations opposite to those of the previously cited publications that showed a higher UIC in spring. The data from the National Neonatal TSH Registry also confirmed seasonal differences in iodine levels and iodine deficiency in Latvia. Increased TSH levels were present in 8.7% of neonates, also indicating inadequate iodine nutrition and being in agreement with the measures of iodine status determined by UIC analysis (Konrade *et al.*, 2014). Nevertheless, the result was significantly better than the rate of 16.5% found during the Latvian Neonatal TSH screening in 2000–2002 (Gyurjyan *et al.*, 2006).

In conclusion, some degree of iodine deficiency is present in 49% of Latvian schoolchildren, especially in urban schools and in the Latgale and Vidzeme regions.

IODINE STATUS IN PREGNANCY

A study of pregnant women in Latvia found a median UIC of 80.8 µg/g Cr, indicating substantial iodine deficiency, and the data supported the notion that iodine deficiency already existed before pregnancy (Konrade *et al.*, 2015). The median UIC was significantly higher in the second and third trimesters, which was attributed to the intake of iodine-containing supplements (Konrade *et al.*, 2015). Contrary to the finding of no seasonality effect in the UIC values, the elevated TPO-Ab concentration was approximately two times higher in spring than in autumn (Konrade *et al.*, 2015). In addition, we did not observe any association between UIC and elevated TPO-Ab values. Because more than 80% of the pregnant women had UICs lower than 150 µg/g Cr, the

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iodine supplementation was not expected to trigger thyroid autoimmunity, a result that has been observed in populations with UICs that were approximately three times greater (Guan *et al.,* 2005). In countries such as Latvia, excessive iodine intake is unlikely, even with regular consumption of iodised salt at the WHO recommended amount of 5 g/day (Anonymous, 2014) and seafood once weekly.

IODIZATION PROGRAMME-RELATED RISKS

The WHO recommended daily dose of iodine is 150 µg for adults, which is approximately three times the amount (52 µg) of iodine that the thyroid must take up daily to remain in balance (Bürgi, 2010). Depending on the availability of iodine, a healthy thyroid gland is able to enhance or limit the use of iodine for thyroid hormone production for a limited period. However, epidemiological studies have linked even a cautious iodisation programme in countries with previous moderate or mild iodine deficiency to the development of hypothyroidism (Pedersen *et al.,* 2007; Li *et al.,* 2008). Furthermore, in almost all cases, this phenomenon had an autoimmune basis (Markou *et al.,* 2001). In this context, previous animal model studies have connected induction of disease processes with thyroglobulin (Tg) iodination, because observations showed that hypo-iodinated Tg did not activate T cells; however, increasing the Tg iodine content to even normal levels *in vitro* led to the antigenicity of the molecule (Barin *et al.,* 2005). Iodide may epigenetically modify the Tg molecule and create iodinated neoantigenic determinants to which immune tolerance has not been established, or it may act via apoptotic/necrotic effects of thyrocytes, thus initiating the presentation of thyroid antigens that can activate T cells (Markou *et al.,* 2001). Whether the pathological process will begin and which pathway will dominate depend on the genetic background.

A sudden increase in iodine intake in an iodine-deficient population may increase thyroid autoimmunity (Kahaly *et al.,* 1998; Pedersen *et al.,* 2007; 2011). One of the best and most studied examples is in Denmark, where iodine fortification of salt was introduced in 1998. In Aalborg, where the median UIC was 45 µg/L at the beginning of the programme, the incidence of hypothyroidism increased; in contrast, in Copenhagen, there was a mild iodine deficiency (61 µg/L) at the beginning of the programme, and the increase was not significant (Pedersen *et al.,* 2007). Overt hypothyroidism occurred most often in young and middle-aged subjects with previous moderate iodine deficiency. Moreover, after five years of the public iodisation programme, the rate of TPO-Ab 30 U/mL in the Danish population increased from 14.3% to 23.8%, and statistical significance was confirmed in multivariate regression models. In this study (Pedersen *et al.,* 2007), the TPO-Ab increase was most pronounced in young women and for the lower antibody concentrations. Nonetheless, the possibility that this result was at least partly a transient phenomenon must be considered (Zimmermann *et al.,* 2003); therefore, further studies are needed to evaluate the long-term effects and clinical consequences.

AN OPTIMAL STRATEGY FOR THE DETECTION OF AUTOIMMUNE THYROID DISEASE IN PREGNANCY

One solution for effective and safe iodine supplementation during pregnancy would be universal screening for autoimmune thyroid disease (AITD) with TSH and TPO-Ab detection at the first antenatal appointment. While the Latvian healthcare system is cutting laboratory testing expenses, such a recommendation would not gain regulatory acceptance. Thyroid, endocrine and obstetrics professional organisations have also prepared position statements on this issue; however, universal screening for thyroid disease during pregnancy is controversial, with strong proponents on both sides (Glinoer, 1998; Casey, 2006; Brent, 2007).

It is evident that thyroid disease has multiple adverse effects during pregnancy and the postpartum period, and in the developing foetus. These effects include miscarriage (Glinoer *et al.,* 1991), preterm delivery (Stagnaro-Green *et al.,* 2005), decreased intelligence quotient (Pop *et al.,* 1999) and visual-motor deficiencies (Zoeller and Rovet, 2004) in the offspring, especially in women with elevated serum antithyroid antibody titres (Stagnaro-Green and Glinoer, 2004). Women with thyroid autoimmunity are also at an increased risk for postpartum thyroiditis (Muller *et al.,* 2001) and the development of overt hypothyroidism in the future (Vanderpump *et al.,* 1995). Despite the lack of effective strategies to decrease maternal and foetal complications for pregnant women with thyroid abnormalities (Negro *et al.,* 2010), most professional associations recommend case finding for pregnant women who are identified as having a high risk for thyroid disease: family or personal history of autoimmune disease, history of neck irradiation, or previous miscarriages or preterm deliveries (Abalovich *et al.,* 2007; Anonymous, 2007). Nonetheless, research data reveal that such practice may miss 30–50% of the hypothyroid cases (Vaidya *et al.,* 2007; Horacek *et al.,* 2010). A literature review found analyses stating that universal screening of pregnant women for AITD is cost effective compared with no screening (Dosiou *et al.,* 2008; Thung *et al.,* 2009). Moreover, studies have shown that universal screening is also highly cost effective compared with high-risk screening only (Dosiou *et al.,* 2012).

According to epidemiological study data, thyroidal autoimmunity affects approximately 11% of women of reproductive age (Hollowell *et al.,* 2002), and this proportion was also observed in Latvia (Konrade *et al.,* 2015). To improve obstetric outcomes and gain child IQ benefits in the setting of established iodine deficiency, a universal screening measuring TSH and TPO-Ab levels would allow personalised iodine supplementation recommendations.

RECOMMENDATIONS

In the absence of a mandatory salt iodisation programme, there is a persisting iodine deficiency among Latvian schoolchildren during the spring season and a noteworthy iodine deficiency in pregnant women in Latvia, which warrant intervention.

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The strategies for increasing the consumption of iodine-containing products to approximately 150 μg should be improved, particularly for children. Therefore, initiatives, such as the School Milk Programme and the use of iodinated salt in both school and household kitchens, will improve iodine nutrition.

Because mild to moderate iodine deficiency during pregnancy and the lactation period can adversely affect foetal brain development, WHO-UNICEF and ICCIDD advise an increase in the recommended daily dosage of iodine to 250 μg/day for pregnant women and breastfeeding women and 150 μg/day for women in the preconception period (Anonymous, 2008).

An adequate iodine status is important even before fertilisation and pregnancy. All women of childbearing age should be advised to increase their dietary iodine intake through the use of iodised table salt and dairy products and the consumption of seafood twice weekly.

Data from a survey of the Latvian population indicate that approximately 100 μg of iodine per day is consumed through foods and iodised salt. To meet the increased iodine requirement in pregnancy, pregnant women should take a supplement containing 150 μg of iodine daily from the earliest time possible.

Breast milk is an important source of iodine to maintain thyroid function in infants, who are highly dependent on maternal iodine nutrition during breast feeding. Therefore, in addition to dietary iodine sources, iodine supplementation of 150 μg daily is recommended for breastfeeding women.

Whilst the importance of gestational iodine supplementation is undisputed, we believe that in mild-moderate iodine-deficient areas, such as Latvia, women considering conception who do not have adequate iodine intake through diet should be advised to consume iodine supplements for several months prior to pregnancy.

Iodine supplements may be contraindicated for women with certain pre-existing thyroid pathologies; the medical decision, which is taken on a case-by-case basis, is made by the physician.

UIC monitoring among schoolchildren and pregnant women and neonatal TSH registry analysis every five years will provide appropriate indicators for iodine intake to help keep UIC values within, but not higher than, the range that prevents IDD.

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JODA DEFICĪTS LATVIJĀ: PAŠREIZĒJAIS STĀVOKLIS UN NEPIECIEŠAMĪBA PĒC JAUNĀM NACIONĀLAJĀM REKOMENDĀCIJĀM

Apstākļos, kad Latvijā nav obligātas sāls jodēšanas programmas, divi nacionālie šķērsgriezuma klasteru apsekojumi atklājuši joda deficītu Latvijas skolēniem pavasara sezonā un būtisku joda deficītu grūtniecēm Latvijā; šis deficīts prasa iejaukšanos. Viegla un mērena joda deficīta sekas grūtniecības un barošanas ar krūti laikā var nevēlami ietekmēt augļa smadzeņu attīstību. Saskaņā ar datiem no Latvijas iedzīvotāju apsekojuma dienā ar ēdienu un jodēto sāli tiek uzņemti apmēram 100 µg joda. Tāpēc būtu nepieciešama stratēģija jodu saturošu produktu patēriņa palielināšanai, it īpaši bērniem. Turklāt, lai sasniegtu palielināto joda pieprasījumu grūtniecības laikā, grūtniecēm pēc iespējas agrāk jāsāk lietot uztura bagātinātājus, kas satur vismaz 150 µg joda. Visām reproduktīvā vecuma sievietēm jāiesaka palielināt joda uzņemšanu ar ēdienu, lietojot jodēto sāli un produktus, kas satur daudz joda: jūras veltes, pienu un piena produktus. Sievietēm ar jau esošu vairogdziedzera slimību medicīniskais lēmums jāizdara katrā gadījumā atsevišķi. Joda koncentrācijas mērīšana urīnā skolēniem un grūtniecēm un jaundzimušo vairogdziedzeri stimulējošā hormona (TSH) reģistra analīze ik pēc pieciem gadiem būtu piemērota stratēģija joda nodrošinājuma uzturēšanai intervālā, kas novērš joda deficīta radītos traucējumus.

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