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Review Article

Value and pitfalls in iodine fortification and supplementation in the 21st century

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Abstract

Although the number of iodine-deficient countries has been reduced by almost 50 % over the last decade, it still remains a frequently misunderstood health problem. The most devastating effects of iodine deficiency occur during fetal development and childhood, periods in which sufficient iodine delivery remains critical. Besides the determination of thyroid size, the concentration of urinary iodine, serum thyroid-stimulating hormone and serum thyroglobulin are useful biomarkers to assess iodine status. Severe iodine deficiency is associated with neurological complications, cretinism, endemic goitre development, hypothyroidism, decreased fertility and increased infant mortality. The recommended iodine supplementation strategies are based on correction of iodine deficiency, close monitoring and evaluation of iodine administration, cooperation of the salt industry, training of local health care professionals and education of the population. Besides the multiple beneficial effects of supplementation, we present in this review a critical look at the possible side effects.

Key words: Iodine deficiency: Fortification: Supplementation

Although the presence of iodine in the thyroid was already discovered in 1895 by Bauman[(1)], it took until 1917 before Marine & Kimball[(2)] could make the connection between iodine deficiency and the occurrence of goitre. An estimated 200–300 million people presently suffer from some form of iodine deficiency, mainly in Asia and Africa, but also in large parts of Eastern Europe[(3)]. Multiple studies have emphasised the influence of ethnicity and seasonality on iodine status[(4–6)]. In general, iodine deficiency in a population is associated with subtle, negative effects: a decreased level of education, reduced work productivity and apathy, disrupted economic and social development. As mild-to-moderate iodine deficiency affects 30 % of the total population and may impair cognitive development in children, iodine deficiency is considered as the most common cause of preventable mental retardation worldwide[(7)]. Adequate iodine intake is particularly important in vulnerable groups, such as pregnant women, lactating women and infants[(8)]. Given the fact that a lack of this essential nutrient is the main cause of preventable brain damage, universal iodine supplementation is part of many national nutritional strategies[(9)]. Mild iodine deficiency is associated with a higher prevalence of autonomous thyroid nodules and multinodular goitre, which are the main causes of hyperthyroidism in the adult population[(10)]. The purpose of the present study was to give an overview of the important role of iodine supplementation without forgetting the pitfalls.

Epidemiology

The prevalence of iodine deficiency is mainly based on data from urinary iodine levels in school children, which generally reflects the status of the entire population[(11)]. However, some authors found major differences in the nutritional profile of children and adults, suggesting that the outcome of the earlier studies might not present an accurate picture of iodine deficiency in the whole population[(6)]. The total prevalence of goitre is not sufficiently sensitive to recent changes in

Abbreviations: KI, potassium iodide; LID, low-iodine diet; PTC, phenylthiocarbamide; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; UI, urinary iodine concentration.

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iodine intake. In 2007, the WHO reported that nearly 2 billion individuals worldwide (36·5 % of school-age population and 35·3 % of the general population) had insufficient iodine intake, including one-third of all school-age children. Until recently there was no system for monitoring iodine deficiency. Unlike the USA, where >90 % of the households use iodised salt, European countries are characterised by a high degree of iodine deficiency (±60 %). Implementation of structured iodine supplementation programmes led to a turnaround in 2003, with a decline in the proportion of school-going children at risk[3]. Presently, the prevalence of goitre globally is 15·8 %, with the highest frequency in the Eastern Mediterranean (37·3 %) and the lowest in the USA (4·7 %)[12]. The interpretation of the WHO data should be done with caution. Representative (sub)national studies covering 60 % of the global population can underestimate or overestimate the extent of iodine deficiency. Extrapolation of a population indicator (the median urinary iodine content) to define the number of affected individuals is also not so accurate[3]. Finally, there are insufficient data available to estimate the prevalence of this health problem in pregnant women[13].

Polymorphism

Although iodine supplementation will aid significantly in ameliorating thyroid problems, evolutionary pressure should also be taken into account. Strong selective pressures in the past have shaped our ability to detect anti-thyroid compounds and to avoid them[14]. Food preferences are influenced by a number of factors such as personal experiences, cultural adaptations and perceived health benefits. Based on the response to bitter-tasting compounds such as phenylthiocarbamide (PTC) or 6-*n*-propylthiouracil, individuals can be classified as supertasters (30 % of the world's population), tasters (50 % of the world's population) or non-tasters (20 % of the world's population)[15–21]. The prevalence of taste insensitivity to PTC and 6-*n*-propylthiouracil varies in human populations: Indians: 40 %, Caucasians: 30 %, Chinese: 6–23 % and West Africans: 3 %[22–23]. Bitter substances bind to approximately thirty human taste receptors type 2, residing on the surface of the taste cells within the taste buds of the tongue. Those receptors belong to the heptahelical or G protein-coupled receptor (GPCR) family, characterised by the presence of seven transmembrane helices and the interaction with intracellular G proteins[24–26]. Activation of the G protein-coupled receptor signalling pathways leads to bitter perception[27]. Polymorphisms of the TAS2R38 gene (located in a small region on chromosome 7q) account for 55–85 % of the variance in PTC sensitivity, which is almost completely explained by amino acid substitutions at position 49 (alanine or proline), 262 (valine or alanine) and 296 (isoleucine or valine)[28]. This gives rise to two major haplotypes (proline–alanine–valine (the taster variant) and alanine–valine–isoleucine (the nontaster variant)) and three less common variants, which are either rare (alanine–alanine–valine and proline–valine–isoleucine) or limited to specific populations (alanine–alanine–isoleucine in sub-Saharan Africans)[29]. Subjects, homozygous for the proline–alanine–valine haplotype are most sensitive to the taste of PTC or 6-*n*-propylthiouracil; those who are homozygous for the alanine–valine–isoleucine haplotype are least sensitive while individuals who carry a copy of both haplotypes (proline–alanine–valine/alanine–valine–isoleucine) have an intermediate sensitivity[30–31].

As PTC-related substances show anti-thyroid activity, a significant excess of non-tasters with non-toxic goitre has been reported in communities with endemic goitre[16,20,21,32]. Ingestion of glucosinolates in plants inhibits thyroid peroxidase activity and blocks active transport of iodide into the thyroid, resulting in both retarded sexual maturation and mental retardation in low iodine regions[33–35]. After iodine supplementation, the described association is no longer observed. It has been suggested that PTC polymorphism is conserved in human beings as a protective mechanism against the overconsumption of dietary goitrogens[32].

Detection methods for iodine deficiency

Four complementary indicators are available for determining iodine status: urinary iodine concentration (UI), thyroid size, serum thyroid-stimulating hormone (TSH) and thyroglobulin (Tg). UI is a sensitive biochemical marker of recent iodine intake (d)[36]. A simple spot urine sample collected from a representative sample is sufficient to measure iodine output (μg/l). Although the median UI gives no direct information on the thyroid function, a low value is an indication of an increased risk for thyroid problems[37]. Iodine excretion may vary on a daily basis, intra-/inter-individually and among different population groups[38]. The thyroid size is primarily determined by inspection and palpation (grade 0–2). Despite the advantages (non-invasive and quick to implement), the reliability of this method is limited by high inter- and intra-observer variations. An additional ultrasound of the thyroid, taking into account the international reference ranges for a normal thyroid size in iodine-sufficient children, is recommended. Changes in goitre development reflect long-term iodine nutrition (months to years)[39]. Serum TSH is dependent on serum concentration of the circulating thyroid hormone. Although slightly elevated levels are observed in iodine-deficient populations, the majority of school children and adults present normal TSH concentrations. The increase in the number of neonates with moderately elevated TSH concentrations (>5 mIU/l in whole blood) is proportional to the degree of iodine deficiency[37,40–42]. Serum Tg concentrations are increased in thyroid hyperplasia and after TSH stimulation. There is a good correlation with the degree of iodine deficiency, measured by UI. Moreover, Tg is also a better indicator for iodine repletion (weeks to months) compared with TSH or T_4[43]. As the widespread use of TSH and Tg in the determination and monitoring of iodine deficiency at the population level is still very limited, these data were not included in the WHO database on iodine deficiency[40].

Iodine fortification and supplementation

The universal iodisation of salt (both for human and animal consumption) is considered as the most appropriate strategy to address the problem of iodine deficiency. Its success has many reasons. Salt is used by almost everyone and its intake is even throughout the year. In most countries, the production and import of salt are carried by a limited number of people. The implementation of a universal salt iodisation is a larger, but still a worthy challenge in areas with many small salt producers. Moreover, it is a simple and cost-effective method, with no change in colour and taste of the salt. The amount of iodine added to salt can easily be monitored[37,44].

The WHO recommends a daily iodine intake of 90 μg for infants (0–59 months), 120 μg for school-age children (6–12 years), 150 μg for adolescents and adults and 200 μg for pregnant and lactating women. Fortification of iodine to salt can occur in the form of potassium iodide (KI) or iodate. Depending on the local salt intake, 20–40 mg iodine/kg salt is added following the guidelines of the WHO/UNICEF/International Council for the Control of Iodine Deficiency Disorders[3]. Environmental factors, such as the consumption of goitrogens and a shortage of trace elements in the diet (Se and Fe), may prevent an optimal response to administered iodine[45,46].

Alternatives to universal salt iodisation have been described. Bread, water, irrigation water, milk and cattle feed are vehicles for iodised salt[47–51]. Iodised oil, obtained by esterification of unsaturated fatty acids in seed or vegetable oils, can be given daily or annually in a peroral or intramuscular administration[3,52,53]. The dose is 200–400 mg iodine/year and is primarily intended for young or pregnant women and children[3]. The administration of iodine in the form of KI (30 mg/month or 8 mg/2 weeks) or potassium iodate drops/tablets is another option[54]. Antiseptics (Lugol solution) are also iodine preparations[37].

In countries with an iodised salt programme, attention must be paid to weaning infants, particularly to those not receiving iodine-containing infant formula milk. Infants are at high risk for iodine deficiency, because their requirements per kg body weight for iodine and thyroid hormone are much higher than at any other time in the life cycle[55,56]. The iodine intake of breastfed infants relies solely on the iodine concentration of breast milk, which, in turn, reflects the mother's iodine status[8]. The highest concentration of iodine is found in colostrum with concentrations of 200–400 μg/l, decreasing to 50–150 μg/l in mature human milk[57,58]. Pre-term infant formulas contain 20–170 μg iodine/l, which may be too low in particular situations to achieve the recommended intake of iodine[59].

Iodine dosage via the enteral or parenteral route is efficient, as oral iodine bioavailability is 90–95 %. However, parenteral solutions contain much less iodine than enteral formulas. In parenterally fed infants and children, with a daily recommended iodine dose of 1 μg/kg, this 50 % iodine intake deficit is corrected by the absorption of iodine through the skin from topical iodinated antiseptics and by the administration of iodine in other infusions[60,61]. In iodine-sufficient adults, with a daily iodine requirement of 70–150 μg, thyroidal iodine stores are often adequate to meet the needs of adult patients requiring total parenteral nutrition for less than 3 months[62].

Besides iodised salt, which is the most important source of iodine worldwide, multiple dietary sources of iodine are of great importance for achieving a sufficient dietary iodine intake. Dietary sources of iodine vary with country and population[63]. The native iodine concentrations in most food groups are low. The most commonly consumed foods provide 3–80 μg/serving[60]. The highest content of this micronutrient is found in milk, eggs and products of marine origin (with higher mean iodine concentrations in lean fish species compared with fatty fish species). Milk and dairy derivates contain relatively high amounts of iodine. A seasonal variation of iodine concentration in milk is reported with a significantly higher iodine content of milk in the winter season, compared with the summer season. This finding can be explained by the use of cow fodder fortified with iodine during winter. The average iodine content within the same season is comparable for different types of milk[63]. In a group of pregnant women, a multivariate analysis showed that milk was the only variable influencing UI, including the use of iodised salt, iodine supplementation and different foods[8]. Moreover, in contrast to fish, eggs or iodised salt, a high correlation between UI, milk and dairy products intake was reported in Italian school children[64]. Eggs, and more specifically egg yolks, are another rich source of iodine. The content of iodine in eggs depends on the iodine concentration in hen fodder[65]. Recently, the value of fortified eggs as a unique nutritional supplement for peak brain development during pregnancy, nursing and infancy was demonstrated[66].

Seafood, including saltwater fish, shellfish, kelp, seaweed and seaweed products can provide a considerable amount of iodine. However, its contribution depends on the alimentary habits of the population[63]. Iodine inhalation may influence iodine status and may help explain why despite the absence of a regular source of dietary iodine intake such as iodised salt, coastal communities residing in seaweed-rich areas can maintain an adequate dietary iodine supply[67].

The mean iodine concentration in other foodstuffs (meat, meat products, bread, cereals, vegetables, potatoes, fruits, berries, fats and oils) is 2–3 μg/100 g, which is limited in comparison with the total iodine intake. The contribution of iodine from drinking-water is region dependent[63]. Iodine-containing compounds used in irrigation, fertilisers, livestock feed, dairy industry disinfectants and bakery dough conditioners influence iodine content in foods[60].

Iodine supplementation by the independent administration of KI is preferable, as a lot of multivitamin preparations do not contain an adequate amount of iodide[67]. Recent studies in Spain have shown that only a minority of women used iodine supplements during their pregnancy, either as iodine or as multivitamin tablets containing 100–200 μg of iodine each. Although iodine supplementation alone was not effective, the combination of iodine supplements and a diet rich in milk reached an acceptable median UI. Pregnant women from an iodine-sufficient area could have a suboptimal iodine status without a diet rich in iodine or without supplementation with iodine-containing tablets[66]. Apart from universal iodisation of salt, the use of iodine supplements as vitamin complexes or as KI tablets is recommended from the start of gestation or earlier in the case of planned pregnancy[68].

Value and pitfalls

Benefits

Pre-natal iodine supplementation in severe iodine deficiency is associated with a significant reduction in the prevalence of endemic cretinism[69]. Data from cross-sectional studies on the relationship between iodine intake and post-natal growth of the child are often contradictory, although most of them describe a positive correlation[70–72]. Iodine repletion induces an increase in insulin-like growth factor 1 and insulin-like growth factor binding protein 3 with a beneficial effect on somatic growth in children from moderate-to-severe iodine-deficient areas[73].

The interpretation of the results of randomised trials, which investigate the impact of iodine supplementation studies on the cognitive functioning of children, is hampered by methodological problems[74]. Targeted supplementation to pregnant women, living in regions with a history of even small degrees of iodine deficiency, needs a strong implementation of pre-conception programmes since the start of pregnancy is often detected at a later stage[75]. Iodine treatment of pregnant women in areas with severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive abilities of the offspring[76,77]. Adequate substitution during the first and second trimester appears to be essential[78,79]. Pre- and post-natal iodine supplementation of Chinese children from areas with severe iodine deficiency resulted in an average increase of 8·7 intelligence quotient points[80]. The recommended cut-off for the median UI in lactating women is 100 μg/l based on the premise that the expression of the sodium iodide symporter in the breast during lactation results in dietary iodine being secreted into breast milk rather than into urine[54,81]. In countries with a sustained iodine supplementation programme, newborns may not be at risk of alterations in thyroid functions, irrespective of mothers' UI[82]. In regions with iodine deficiency, the breast-milk iodine concentration appears to decrease over the 24-week postpartum period, indicating that the amount of iodine in breast-milk needs to be much higher during early lactation[8].

Several European randomised trials of iodine supplementation were carried out in mild-to-moderate iodine-deficient pregnant women. Iodine reduced the thyroid size of the mother and the newborn. In some cases, a decrease of maternal TSH and Tg was observed. However, no trial showed an effect on total or free thyroid hormone concentrations of the mother and the newborn. Moreover, there was no account of the long-term clinical consequences, such as maternal goitre, thyroid autoimmunity or the development of the child[83–85]. Thyroid autonomy is a frequent cause of thyrotoxicosis in patients with iodine deficiency. Based on epidemiological data, which suggest an influence of iodide on the course of pre-existing thyroid autonomy[86], Müller *et al.*[87] investigated the effect of iodine on early-stage thyroid autonomy. In cell cultures, iodine decreases the biological activity of autonomous thyrocytes. Iodine supplementation prevents the development of thyroid autonomy by decreasing the occurrence of somatic TSHR mutations and slows down the development of clinically relevant disease. Recently, the influence of iodine supplementation on thyroid function and its effect on plasma markers of oxidative stress, inflammation and acute-phase proteins was examined in a population of healthy adults with adequate iodine intake. The administration of 100–300 μg iodine in the form of KI for 6 months did not modify thyroid function. Moreover, a slight anti-inflammatory and antioxidative action of iodide was demonstrated[88].

The economic advantages for health of avoiding endemic goitre and mental retardation in the case of severe iodine deficiency are quite obvious. In addition, implementation of an iodisation programme in a country suffering from mild iodine deficiency can be considered, which may prevent hyperthyroidism by reducing the number of patients with multinodular goitre and thyroid nodules and may improve cognition in mildly iodine-deficient children[3,89–91].

Abundance and toxicity (Table 1)

The thyroid gland is able to adapt to different doses of iodine to regulate the synthesis and release of thyroid hormones. A chronic intake of 30 mg up to 2 g iodine/d is tolerated by iodine-sufficient individuals. A persistent drop of serum T_4 and T_3 of 25 and 15 %, accompanied by a TSH rise of 2 mIU/l is observed. An excessive intake of iodine may increase the risk of autoimmune thyroiditis, hyperthyroidism (especially in a pre-existing multinodular goitre), (sub)clinical hypothyroidism (especially in a pre-existing Hashimoto's thyroiditis) and goitre[92,93].

One of the main side effects seen in multiple iodine supplementation programmes concerns iodine-induced hyperthyroidism[94–96]. The risk is elevated in an initial severe iodine deficiency, a subsequent (too) large increase in iodine intake, a mean urinary iodine level ≥300 μg/l and in smokers[10,96]. Especially, adults (>40 years) with a long-standing nodular goitre are at increased risk. Given that the symptoms of iodine-induced hyperthyroidism are not specific enough, this problem is frequently overlooked[97]. Iodine-induced hyperthyroidism is almost always transient and the incidence falls over time (1–10 years after the introduction of the supplementation programme) back to its normal level[98]. An excessive intake of iodine may induce a flare of Graves' disease, which is age independent[99]. Besides the effect on thyroid hormone synthesis, this is most probably due to the stimulation of the intra-thyroidal autoimmune process. However, autonomous nodules are not the only pathogenetic explanation for iodine-induced hyperthyroidism, as this phenomenon was also reported in entirely normal glands[100].

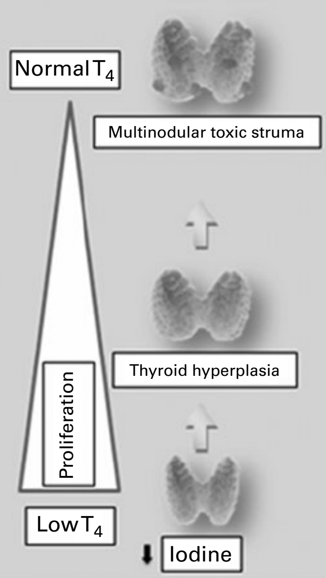
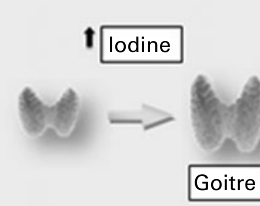
Bülow Pedersen *et al.*[101] diagnosed new cases of hypothyroidism in addition to hyperthyroidism. Despite a careful introduction of iodised salt, the incidence of hypothyroidism slightly increased in areas with a previous moderate iodine deficiency. Even in subjects with normal thyroid function, high iodine intake can negatively affect thyroid hormone levels[102]. Investigation of the impact of iodine intake on thyroid diseases in China showed an increase in the prevalence of overt hypothyroidism, sub-clinical hypothyroidism and autoimmune thyroiditis with increasing iodine intake[103].

In addition, the investigators showed in a recent paper that even a median UI of 200–300 μg/l might be related to a potential increased risk of developing sub-clinical hypothyroidism or autoimmune thyroiditis[104], which differs from the data published by the WHO (median UI > 300 μg/l)[40]. The exact mechanism by which chronic high iodine intake induces hypothyroidism remains unclear. Iodine-induced hypothyroidism usually resolves quickly after iodine withdrawal, but if the administration of iodide continues, overt or sub-clinical hypothyroidism will persist[105]. Preventing iodine deficiency-induced hypothyroidism is important as it is an independent risk factor for CHD and can result in a poor neurodevelopmental outcome if present during pregnancy[106,107]. A more than adequate iodine intake may be a risk factor for autoimmune thyroiditis in humans, which is reflected by the correlation between the prevalence of positive thyroid autoantibodies and the amount of iodine intake. The underlying mechanisms of this phenomenon induced by iodine intake are: (1) an increased immunogenicity of Tg, precipitating an autoimmune process at both the T and B-cell level; (2) a toxic effect on thyroid cells and (3) a direct stimulation of immune and immunity-related cells[104].

Acute iodine poisoning, which is uncommon as it usually occurs with doses of multiple grams, is associated with gastrointestinal discomfort (abdominal pain, nausea, vomiting and diarrhoea), cardiovascular symptoms, coma and cyanosis. An excessive intake of iodine may rarely cause iodermia, a dermatological condition comprising acneiform eruptions, an itchy rash and urticaria[108,109]. Iodine excess causes a temporary inhibition of thyroid hormone synthesis (the Wolff–Chaikoff effect), inhibits cell growth, induces apoptosis and affects cell morphology[110].

Although animal studies showed a significantly increased number of thyroid carcinomas after prolonged iodine deficiency, proof of a direct causative role for iodine deficiency remains elusive. A review of animal experiments, epidemiological and basic gene transfection studies showed a weak relationship between iodine intake and cancer[111].

Table 1. Classification according to the degree of iodine deficiency

Iodine intake	Iodine status	Median urinary iodine concentration (μg/l)	Consequences	Pathophysiology
Insufficient	Severe iodine deficiency	<20	Goitre, multinodular toxic stroma, increased incidence of thyroid carcinomas	
	Moderate iodine deficiency	20–49	Pregnancy: Gestational hypertension, first trimester abortion, stillbirth, congenital defects, impaired mental and psychomotor development of the fetus	
	Mild iodine deficiency	50–99	Chronic iodine deficiency: Dyslipidaemia, insulin resistance, subclinical inflammation	
Sufficient	Normal iodine status	100–199		
Excessive	Moderate overdosage	200–299	Autoimmune thyroiditis, hypothyroidism or hyperthyroidism, goitre, Graves' exacerbation, decreased treatment efficacy with radioactive iodine	
	Excessive overdosage	≥300	Risk of adverse health consequences (autoimmune thyroiditis, hyperthyroidism, (sub) clinical hypothyroidism and goitre)	

The overall incidence of differentiated thyroid carcinoma is generally not considered to be influenced by iodine intake of a population, whereas the distribution of the types of thyroid carcinoma (papillary:follicular carcinoma ratio) seems to be related to the intake of iodine. Papillary carcinoma is the predominant type of thyroid malignancy in non-endemic areas and shows an increasing incidence in goitrous regions after iodine prophylaxis. This could be related to the long-term effect of iodine supplementation and/or to other factors (e.g. radiation fallout, inclusion of papillary microcarcinomas, better access to medical care, etc.)[112–114]. Iodine-deficient regions have a tendency to show higher rates of undifferentiated (anaplastic) carcinomas before iodine prophylaxis, compared with post-prophylaxis periods and regions with high dietary iodine intake[114].

In the treatment and follow-up of well-differentiated thyroid cancer, a temporary low-iodine diet (LID) is generally recommended before high-dose radioactive iodine (^{131}I) ablation therapy or radioactive iodine scanning. The stringency and the duration of restriction about the time of therapy are debatable[115]. The American Thyroid Association recommends an LID defined by an intake of $<50\,\mu$g/d for 1–2 weeks before ^{131}I ablation[116]; the British Thyroid Association recommends an LID for 2 weeks before ^{131}I ablation or therapy[117]; the European Thyroid Cancer Taskforce recommends an LID for 3 weeks before ^{131}I administration[118] and the American Association of Clinical Endocrinologists recommends consumption of an LID for 2–4 weeks before radioiodine scanning, with no specific recommendations on stringency or diet before ^{131}I treatment. It is currently not known whether an LID may result in improved long-term outcomes in thyroid cancer[115].

Discussion

Iodine deficiency is the leading global cause of preventable brain damage. It remains the primary motivation behind the present global approach to eliminating iodine deficiency. Although multiple studies have stressed the importance of iodine supplementation, we also need to be mindful of its risks. The intake of iodine from a base diet varies considerably between countries, mainly due to a different consumption of milk and dairy products, bread, marine fish and iodised salt. In multiple studies, the introduction of major salt iodisation programmes was followed by a considerable decrease in the prevalence of goitre and iodine deficiency disorders, saving costs of curative medicine[119]. Approximately, 90 % of salt consumption in industrialised countries is obtained from processed foods, which stresses the importance of using iodised salt in the food industry[120]. However, salt consumption remains a risk factor for hypertension, atherosclerosis, myocardial infarction, stroke and cancer. Verkaik-Kloosterman *et al.* investigated the influence of a reduction in salt intake on habitual iodine intake and subsequent consequences on iodine levels in The Netherlands. Using a simulation model, the investigators demonstrated that despite salt reduction in industrially processed foods of 12, 25 and 50 %, iodine intake remained adequate for a large part of the Dutch population. Only up to 10 % of the subjects would be prone to an inadequate iodine intake if both industrially and discretionary added salt would be reduced by 50 %. The situation is different for the group of 1- to 3-year-old children, which might have an inadequate iodine intake below the corresponding estimated average requirement, depending on the salt intake scenario[121]. However, there is no conflict between the efforts to reduce salt consumption to prevent chronic diseases (even if per capita salt intakes are reduced to <5 g/d) and the policy of salt iodisation to eliminate iodine deficiency[120]. The use of other iodine-rich products (e.g. milk) and iodine supplements to achieve an adequate physiological iodine level must be promoted with individual, population and regional differences in mind[122]. For instance, as a relationship between high iodine level in drinking-water and goitre prevalence has been reported in multiple studies, it can be important to prevent goitre through stopping the provision of iodised salt and providing normal drinking-water iodine in some areas[123–125].

The main constraints to iodine supplementation are related to supply and awareness of health staff and communities[125]. The potential benefits of iodine fortification and supplementation greatly outweigh the potential risks. However, increasing iodine intake in deficient populations is not without risk. Mild iodine deficiency may be associated with a decreased risk of overt and sub-clinical hypothyroidism, as well as autoimmune thyroiditis. A geographical difference in clinical effects of varying iodine intake is observed, which may be related to differences in underlying thyroid autonomy, genetic susceptibility or other environmental variables[37,126]. Efforts to monitor iodine status and to implement adequate iodine supplementation should be intensified in those countries where iodine deficiency remains a public health problem.

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