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Iodine Supplementation
Benefits Outweigh Risks

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Abstract

In 1990, iodine deficiency affected almost one-third of the world population and was the greatest single cause of preventable brain damage and mental retardation. Following a resolution adopted by the World Summit for Children in 1990, major programmes of iodine supplementation were implemented by the governments of the affected countries with the support of major donors. Iodisation of salt was recognised as the method of choice. Nine years later, by April 1999, 75% of the affected countries had legislation on salt iodisation and 68% of the affected populations had access to iodised salt. The prevalence of iodine deficiency disorders decreased drastically in most countries and the deficiency disappeared completely in some such as Peru. This result constitutes a public heath success unprecedented with a non-infectious disease.

However, occasional adverse effects occurred. The principle effect is iodine-induced hyperthyroidism which occurs essentially in older people with autonomous nodular goitres, especially following iodine intake that is too rapid and of too massive an increment. The incidence of the disorder is usually low and reverts spontaneously to the background rate of hyperthyroidism or even below this rate after 1 to 10 years of iodine supplementation. The possible occurrence of iodine-induced thyroiditis in susceptible individuals has not been clearly demonstrated by large epidemiological surveys. Iodine supplementation is followed by an increased prevalence of occult papillary carcinoma of the thyroid discovered at autopsy but the prognosis of thyroid cancer is improved due to a shift towards differentiated forms of thyroid cancer that are diagnosed at earlier stages.

Iodine-induced hyperthyroidism and other adverse effects can be almost entirely avoided by adequate and sustained quality control and monitoring of iodine supplementation which should also confirm adequate iodine intake.

Available evidence clearly confirms that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation.

Iodine is required for the synthesis of thyroid hormones. Thyroid hormones play a decisive role in the metabolism of most human cells and in the process of early growth and development of most organs, especially of the brain. Brain development occurs in humans during the fetal and early postnatal life. Consequently, iodine deficiency, if severe enough to affect thyroid hormone synthesis during this critical period, will result in hypothyroidism and brain damage. The clinical consequence will be mental retardation.[1,2]

The recommended dietary intake of iodine is 50 μg/day from 0 to 12 months of life, 90 μg/day from 1 to 6 years, 120 μg/day from 7 to 10 years, 150 μg/day

during adolescence and adulthood and 200 to 300 µg/day during pregnancy and lactation.[3] When these physiological requirements are not met in a given population, a series of functional and developmental abnormalities occur including thyroid function abnormalities and when iodine deficiency is severe, endemic goitre and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death and infant mortality. These complications, which constitute an hindrance to the development of the affected populations are grouped under the general heading of iodine deficiency disorders.[4]

It was estimated that in 1990, at least 1 572 000 000 people in 118 countries were at risk of iodine deficiency disorders, i.e. these people lived in areas where the total goitre rate was at least 5%. At least 655 million of them, i.e. 12 % of the global population of the world were affected by goitre. 43 million were significantly mentally handicapped as a result of the deficiency, including 11.2 million with overt cretinism.[5] Therefore, iodine deficiency was seen as the greatest single cause of preventable brain damage and mental retardation.

Knowledge of the impact of iodine deficiency on intellectual development and the resulting costs to society, including delayed socioeconomic development, has played a significant role in mobilising scientists, public health administrators and political leaders to deal effectively with iodine deficiency disorders.

1. Benefits of Eliminating Iodine Deficiency Disorders

The sustainable elimination of iodine deficiency disorders by the year 2000 was accepted as one of the priorities in the field of nutrition by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in 1990, and this goal was further endorsed by the World Summit for Children during the same year.

In a first phase of emergency, programmes of iodine supplementation were organised in the most severely affected areas by the administration of slowly resorptive iodised oil, initially given intramuscularly and subsequently by the oral route. These programmes resulted in a drastic reduction of the prevalence of goitre and in the elimination and prevention of endemic cretinism, the most severe complication of iodine deficiency.[6]

In the long term, universal salt iodisation (USI), defined as fortification of all salt for human and animal consumption and for the food industry, was recognised as the method of choice for the prevention of iodine deficiency disorders.[5]

Following the commitments made in 1990, major programmes of salt iodisation were implemented around the world. A close collaboration between UNICEF, WHO, the World Bank, Kiwanis International, bilateral agencies, the iodised salt industry, the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and other nongovernmental international organisations has played a crucial role in supporting national governments in their effort to reach the goal of sustainable elimination of iodine deficiency disorders as a cause of brain damage by the year 2000. In April 1999, 75% of the 130 countries then recognised as at risk of iodine deficiency disorders had legislation on salt iodisation, 73% monitored the quality of iodised salt, 61% monitored the iodine status of the populations and 68% of the affected populations had access to iodised salt. The highest percentage of coverage was found in South and Central America (90%) followed by the South-East Asia region (70%). Of the 8 most populous countries with iodine deficiency disorders (Bangladesh, Brazil, China, India, Indonesia, Nigeria, Pakistan and the Russian Federation), all but 2 have made significant progress towards achieving USI.[7]

These campaigns resulted in a spectacular decrease in the prevalence of iodine deficiency disorders. The change is evident in countries where a longitudinal follow-up has been organised before, during and after the implementation of USI. Selected examples are China,[8] Poland,[9] Iran[10] Bhutan, Cameroon and Peru.[11] A significant decrease in the prevalence of goitre was also observed even in countries with difficult geographical and socioeconomic situations such as the Democratic

Republic of Congo,[12] other African countries,[13] and Central and Eastern Europe.[14] On the other hand, it has been estimated by UNICEF that the number of children born each year at risk of mental impairment due to iodine deficiency decreased from 40 million in 1990 to 28 million in 1997.[15] Additional benefits of iodine supplementation have been a shift of the intellectual quotients of school children towards normal values,[16] an increase in the yield of production of meat, milk and wool by domestic livestock[17] and major savings in the costs of curative medicine.[18] It was estimated that the prevention of iodine deficiency disorders by USI represents a cost of not more than $US0.05 per person every year.[18]

Thus, the benefits of iodine supplementation are considerable from public health and socioeconomic points of view.

2. Risks of Elimination of Iodine Deficiency Disorders

It is important to note, however, that an acute increase in iodine intake where there is chronic iodine deficiency carries risks.[19-21] Allergy to iodine is a theoretical but almost non-existent possibility. The most serious and common complication of salt iodisation is the development of iodine-induced hyperthyroidism, which affects mainly older people with nodular goitres. Other possibilities are the aggravation or even the induction of autoimmune thyroiditis and a change in the pattern of thyroid cancer. In theory, iodine excess can also induce hypothyroidism by acute blockage of the synthesis and secretion of thyroid hormones,[21] but this complication has not been reported with salt iodisation. Similarly, hypothyroidism is extremely rare after the administration of massive doses of iodine in the form slowly resorptive iodised oil, even among pregnant women and neonates.[22]

2.1 Iodine-Induced Hyperthyroidism

Iodine-induced hyperthyroidism is the main complication of iodine prophylaxis. It has been reported in almost all iodine supplementation programmes.[23] The outbreak most thoroughly investigated occurred in Tasmania in the late 1960s and followed supplementation by iodine tablets and iodised bread and the use of iodophors by the milk industry.[24] The incidence of hyperthyroidism increased from 24 per 100 000 in 1963 to 125 in 1967. The disease occurred most frequently in individuals over 40 years of age with multinodular goitres and pre-existing heart diseases. The most severe manifestations were cardiovascular. There was no evidence of any pathogenic mechanism for the Tasmanian epidemic other than iodine deficiency. The epidemic lasted for some 10 to 12 years and was followed by an incidence of hyperthyroidism somewhat below that existing prior to the epidemic. Similar, although much less spectacular experiences of iodine-induced hyperthyroidism in the US, Brazil, Argentina, Ecuador, Chile, Austria, Nepal and Sarawak are described in detail elsewhere.[23] Recently, the introduction of iodised salt in Zimbabwe resulted in a sharp increase over 18 months in the incidence of iodine-induced hyperthyroidism from 3 per 100 000 to 7 per 100 000 inhabitants.[25] Biochemical hyperthyroidism was also reported in selected high risk adults with large goitres in the Democratic Republic of Congo.[26] A multicentre study conducted in 7 African countries including Zimbabwe and Democratic Republic of Congo showed that the occurrence of iodine-induced hyperthyroidism in these 2 countries was due to the sudden introduction of poorly monitored and excessively iodised salt in populations who had been severely iodine deficient for very long periods, resulting in acute iodine overload.[13] As with the previous incidents, the number of new cases of iodine-induced hyperthyroidism in Zimbabwe started to decline after 3 years. These painful experiences underline the importance of monitoring the salt-iodisation process and the supplementation programmes. Recommendations on salt iodisation and monitoring have been updated.[27]

Iodine-induced hyperthyroidism following iodine supplementation cannot be entirely avoided even when supplementation uses only physiological amounts of iodine. In a well controlled longi-

tudinal study in Switzerland[28] the incidence of hyperthyroidism increased by 27% during the year after the iodine supply was increased from 90 μg/day to the recommended value of 150 μg/day. Subsequently, there was a steady decrease in the incidence of the disorder which became lower than it used to be before the increase in iodine intake. More recently, the daily administration of a physiological dose of 200μg iodine to 32 young adults with simple goitre and iodine deficiency (urinary iodine of 32 μg/day) resulted in mild and transient hyperthyroidism in one of them.[29]

The reason for the development of iodine-induced hyperthyroidism after iodine supplementation has now been identified: iodine deficiency increases thyrocyte proliferation and mutation rates.[30] A possible consequence is the development of nodules in the thyroid. Measurement of total intrathyroidal iodine by means of x-ray fluorescence scanning showed that only some nodules keep their capacity to store iodine, become autonomous and result in hyperthyroidism after iodine supplementation.[31] Therefore, iodine-induced hyperthyroidism is an iodine deficiency disorder. It appears to be largely unavoidable in the early phase of iodine supplementation. It affects principally the elderly with long lasting autonomous nodules. Its incidence reverts to normal or even below normal after 1 to 10 years of iodine supplementation.

2.2 Thyroiditis

Another possibility is the aggravation or even the induction of autoimmune thyroiditis by iodine supplementation. Attention was drawn to this possibility when McConahey et al.[32] reported a rise from 0.1% in 1930 to 13% in 1959 in the frequency of Hashimoto's thyroiditis seen in goitres removed in the Mayo Clinic, US. A similar observation was made in Michigan, US.[33,34] In the latter area, the introduction of iodine prophylaxis in the early 1920s seemed likely to be the only variable which might explain the increasing frequency of lymphocytic infiltration seen in thyroid histology. Finally, a higher frequency of thyroid lymphocytic infiltration at autopsy has been reported after the implementation of iodine prophylaxis in Argentina and Ecuador.[35,36]

In experimental conditions, excessive iodine intake can precipitate spontaneous thyroiditis in genetically predisposed strains of beagles,[37] rats[38,39] or chicken.[40-42] The mechanisms involved in iodine-induced thyroiditis in animal models could be[43] that elevated dietary iodine triggers thyroid autoimmune reactivity[44] by increasing the immunogenecity of thyroglobulin or by inducing damage of the thyroid and cell injury by free radicals.[41,43,45]

To the best of our knowledge, to date no large epidemiological, metabolic or clinical surveys have been performed which have analysed the impact of large scale programmes of iodine supplementation on the occurrence of clinically significant iodine-induced thyroiditis with public health consequences on thyroid function. One of the reasons is that the diagnosis is difficult: it is usually based on the presence of thyroid autoantibodies and the echographic pattern. But the number of patients with thyroid autoantibodies without thyroid disease and with an abnormal echo pattern but without lymphocytic infiltration is not known.

Concern about the possible occurrence of thyroiditis after correction of iodine deficiency developed after clinical investigations were conducted in Greece in an endemic goitre area where thyroid autoantibodies were not reported before iodine supplementation.[46] In 58 patients with endemic goitre from this area, thyroid autoantibodies were negative before therapy but became positive in 13 of them 6 months after the intramuscular injection of 1ml of iodised oil containing 480mg iodine.[47] In another study in the same area, 4 of 37 patients also developed thyroid autoantibodies 9 to 12 months after the administration of tablets containing 150μg thyroxine (T4) and 115μg potassium iodide (KI).[48] No clinical consequences were reported.

More recently, Kahaly et al.[29] reported the development of antiperoxidase and thyroglobulin antibodies in 6 out of 31 patients (19%) with endemic goitre treated during 6 months with a supra-

physiological dosage of 500μg KI per day. Mild hypo- or hyperthyroidism developed in 4 of them. The hypo- and hyperthyroidism remitted spontaneously after withdrawal of iodine.

In contrast with these observations, no thyroid autoantibodies appeared in 114 iodine deficient school-age children in Romania during a follow-up period of 1 year after the oral administration of iodised oil containing 200mg iodine.[49] Similarly, the daily administration of 300μg KI per day during pregnancy in 38 women living in an iodine deficient area was not followed by the occurrence of thyroid autoantibodies from 2 to 21 days after delivery.[50]

Laurberg et al.[51] in their detailed comparative epidemiological study of thyroid abnormalities in the elderly in Iceland with a normal iodine intake (median urinary iodine of 150 μg/L) and in Jutland in Denmark with moderate iodine deficiency (median urinary iodine of 38 μg/L) reported that the frequency of thyroid autoantibodies (antiperoxidase and antithyroglobulin) were twice as common in Jutland as in Iceland. The population with the highest prevalence of autoantibodies had a high prevalence of goitre but was not characterised, in general, by high thyroid-stimulating hormone levels. Similarly, Aghini-Lombardi et al.[52] reported that in a community of Southern Italy with mild iodine deficiency (median urinary iodine of 55 μg/L), the detection of low titres of autoantibodies was relatively frequent (12.6%) but that only 3.5% also had the thyroid echographic pattern of diffuse hypoechogenicity that is indicative of diffuse autoimmune thyroiditis, a prevalence that is no different from that observed in iodine sufficient areas.

For the authors, of this last study,[52] thyroid autoantibodies appear as markers but not inducers of thyroid disease, i.e. they are the consequence of the goitre rather than its cause.

It can be concluded from these different studies that there is no evidence that iodine supplementation of a population is associated with a significant risk of autoimmune thyroiditis with clinical consequences in nonsusceptible individuals. However, it is recognised that this conclusion should be supported by more systematic and extensive studies.

2.3 Thyroid Cancer

The relationship of thyroid cancer and endemic goitre has often been debated without agreement being reached on many aspects. There is a tendency for higher incidence rates in autopsy material from endemic goitre areas.[53] The chronic stimulation of the thyroid by thyroid-stimulating hormone is known to produce thyroid neoplasms.[54] The question arises whether the actual incidence of thyroid cancer is higher or if only the mortality of thyroid cancer is elevated. A higher incidence of cancer in iodine deficient areas has been challenged by the classical study of Pendergras[55] who reported a similar incidence of thyroid cancer in goitrous and nongoitrous areas of the US.

Iodine supplementation is accompanied by a change in the epidemiological pattern of thyroid cancer with an increased prevalence of occult papillary cancer discovered at autopsy.[36,56-58] However, the prognosis of thyroid cancer is significantly improved due to the shift towards differentiated forms of thyroid cancer that are diagnosed at earlier stages. Moreover, careful monitoring of the incidence of thyroid cancer in Switzerland following iodine supplementation showed that this incidence steadily decreased from 2 to 3 per 100 000 in 1950 to 1 to 2 per 100 000 in 1988.[59] It would be hazardous to conclude that iodine supplementation reduces the incidence of thyroid cancer but it can probably be stated that this supplementation does not result in an increase in the incidence.

3. Conclusion

The progress towards correction of iodine deficiency globally in the past decade is a public health success unprecedented with a non-infectious disease. The experience shows that the goal is achievable, that the means of achieving the goal are good and that the political commitment is present in most affected countries. This review confirms clearly that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplemen-

tation.[20,60-62] Iodine-induced hyperthyroidism and other adverse effects can be almost entirely avoided by adequate and sustained quality assurance and monitoring of iodine supplementation, which should also confirm adequate iodine intake.

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