Physiopathology of Iodine Nutrition

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Iodine is an essential trace element whose only confirmed function concerns the formation of thyroid hormones. Our knowledge of the disorders caused by deficiencies in the dietary supply of many trace elements has markedly increased only during the last decade. Iodine is one exception to this rule. The role played by iodine deficiency in the etiology of disorders of the thyroid gland and in particular of endemic goiter has been documented for almost two centuries (1). Yet endemic goiter affects at least 300 million human beings in the world and still constitutes one of the major public health problems in the field of nutrition (2).

This chapter reviews disorders resulting from iodine deficiency. It is shown that these disorders are found today not only in developing countries but also in industrialized countries in Europe, particularly in young infants.

PHYSIOLOGY OF IODINE NUTRITION

Cycle of Iodine in Nature

Iodine present in the original earth has been gradually leached away from surface soil by rain and carried out to the oceans by rivers. It evaporates from the ocean water to the atmosphere, is then concentrated in the rain, and falls back to the earth where it replenishes the soil (3). It is estimated that every year about 400,000 tons of iodine escape from the oceans. Sea water contains an average of 50 μg of iodine/liter, atmospheric air about 0.5 μg/liter, and rain and river water about 5 μg/liter. The iodine content of the soil fluctuates greatly.

The main source of iodine for human consumption is food. Drinking water constitutes a poor and insufficient source of iodine. The highest iodine content is found in seafoods, in which it can be as high as 800 μg iodine/kg. The other main dietary sources of iodine are eggs, meat, milk, and cereals. The content varies considerably from one region to another and from season to season, especially in milk products. Many additives markedly increase the iodine content of food, e.g., iodate as dough conditioner in the bread industry and iodoform in water as disinfectant.
Iodine Requirement in Humans

The physiological requirement of iodine is difficult to ascertain and has given rise to much controversy (4). It must be at least equal to the daily amount of hormonal iodine degraded in the peripheral tissues and unrecovered by the thyroid, i.e., 40 to 100 μg/day (5). This is why some authors recommend iodine intake of the order of 100 μg/day for adults (6) and smaller, gradually increasing amounts for children. In 1974 the Food and Nutrition Board of the National Academy of Sciences, National Research Council, United States recommended (7) a daily iodine intake of 35 μg/day for children aged 0 to 6 months, 45 μg/day for those 6 to 12 months, 60 to 110 μg/day for those 1 to 10 years, and 100 to 115 μg/day for those 11 years and more. The recommended intakes during pregnancy and lactation were 125 and 150 μg/day, respectively. For man, the optimum intakes are 10 to 20% higher than for women from the onset of puberty, with a maximum of 150 μg between the ages of 15 and 18 years.

Wayne et al. (8) calculated the iodine intake needed to keep the plasma iodide level (PII) from falling below the critical limit of 0.10 μg/dl, which is used as the sign of a state of iodine deficiency likely to cause the onset of goiter. Allowing for a renal iodide clearance of 34 ml/min and a fecal iodide loss of some 20 μg/day, they calculated the minimum iodine requirement to be 120 μg/day in adults and proposed as safe figures 160 μg/day during adolescence and 200 μg/day for pregnancy and lactation. Higher rates, however, in the region of 200 to 300 μg/day are recommended by other authors (9,10), and still higher iodine intakes of as much as 500 to 800 μg/day have been observed in some parts of the United States (9–12). Epidemiological and metabolic data suggest that an iodine intake of this higher order of magnitude is of negligible benefit in preventing goiter: During large-scale epidemiological studies in Central America (13) it was shown that the prevalence of goiter was extremely high when the iodine intake was below 40 μg/day, falling to less than 10%, a figure regarded as normal by the World Health Organization (14), when the iodine intake reached the critical limit of 100 μg/day, and that a further increase from 100 to 500 μg/day made no significant reduction in the prevalence of goiter. Moreover, the level of iodine contained in the thyroid as hormonal iodine, which is the determining factor in the origin of the disorders characteristic of endemic goiter (15), was low, with an iodine intake below 50 μg/day, but reached a normal value of 10 to 20 μg when the iodine intake reached the same critical threshold of 100 μg/day. It showed virtually no further increase with intakes varying from 100 to 300 μg/day. Similar findings were observed in regard to the absolute uptake of iodide by the thyroid and hormone secretion (16).

In line with the information given above, the Pan American Health Organization proposed (4) that salt be systematically iodized in regions where endemic goiter is a public health problem and recommended a salt iodization rate of 1/10,000 to 1/30,000, so that, assuming a daily salt consumption of about 5 to 15 g/person, the daily iodine intake would be about 150 to 300 μg/day.
IODINE NUTRITION

HYPERSENSITIVITY OF THE NEWBORN TO IODINE DEFICIENCY

Severe Iodine Deficiency

There are enormous areas in the world today where the iodine supply of the population is clearly deficient and which are affected by endemic goiter and its main complication, endemic cretinism (2). These areas are usually found in the mountains because the soils poorest in iodine, which therefore are likely to be areas of endemic goiter, are those which were longest covered by the quaternary glaciers whose melting leached most of the iodine from the ground beneath. The most important areas of endemic goiter in the world today are found in the Himalayas and the Andes. However, other areas also affected by iodine deficiency and endemic goiter are found in the tropical forest covering the central part of Africa. These areas are far from the sea, and consequently the iodine content of rainwater is negligible.

Iodine is a major constituent of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). These hormones are synthesized within the thyroid gland from thyroglobulin, an iodinated glycoprotein contained in the colloid of the thyroid follicles. The primary consequence of iodine deficiency is to decrease the synthesis and release of thyroid hormones by the thyroid gland, resulting in low concentrations of thyroid hormones in the serum. This stimulates the feedback mechanism involving the thyroid–hypothalamus–pituitary axis and results in increased secretion of thyrotropin (TSH) by the pituitary. This state of hyperstimulation by TSH results on the one hand in stimulation of all steps of iodine metabolism and on the other hand in stimulation of the growth of thyroid tissue and the development of goiter (17).

Table 1 shows the typical biochemical picture observed in severe endemic goiter. In the Ubangi endemic goiter area in northwestern Zaire, the iodine intake is only 15 µg/day, the prevalence of goiter is 76.8% of the total population, and 1 to 5%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Brussels Adults (Mean ± SEM)</th>
<th>Ubangi Clinically euthyroid (n=125)</th>
<th>Myxedematous cretins (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentration</td>
<td></td>
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<tr>
<td>T4 (µg/dl)</td>
<td>8.1 ± 0.1 (125)*</td>
<td>4.9 ± 0.2 (358)</td>
<td>0.50 ± 0.01 (120)</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>144 ± 3 (124)</td>
<td>166 ± 3 (299)</td>
<td>46 ± 3 (109)</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.7 ± 0.1 (125)</td>
<td>18.6 ± 2.1 (365)</td>
<td>302.7 ± 20.0 (122)</td>
</tr>
<tr>
<td>Thyroid uptake of 131I</td>
<td>46.4 ± 1.1 (255)</td>
<td>65.2 ± 0.9 (167)</td>
<td>28.3 ± 2.6 (6)</td>
</tr>
</tbody>
</table>

24 hr (% dose)

*a*Modified from Delange et al. (18); results are given as mean ± SEM.

*b*The numbers of patients are shown in parentheses. The differences for each variable between groups are highly significant (p < 0.001).
of this population have clinical signs of severe and long-standing hypothyroidism with mental retardation, dwarfism, and myxedema. These patients are called myxedematous endemic cretins (18). Table 1 shows that, compared to Belgian controls, clinically euthyroid inhabitants of this area have lower $T_4$ and higher TSH levels. They also have higher $T_3$ and thyroidal uptake of radioiodine. In contrast, clinically hypothyroid cretins are also biochemically hypothyroid with almost undetectable serum levels of thyroid hormones and extremely elevated serum TSH levels.

Additional investigations conducted in the same area have shown that thyroid function is much more severely and frequently impaired in newborns than in adults (19,20): The frequency distributions of serum TSH and $T_4$ in cord blood have been compared in Brussels and in the Ubangi area. In the endemic goiter area, both cord serum TSH and $T_4$ showed an important variability between individuals, and only 70% of the values were situated within the normal range for Brussels. The most important observation in this study was that as many as 11% of the newborns of the Ubangi area had both a cord serum TSH above 100 $\mu$U/ml and a cord serum $T_4$ level below 3 $\mu$g/dl, which is a biochemical picture of severe congenital hypothyroidism according to western standards. Consequently, the frequency of thyroid failure in this area was still 10 times higher in newborns than in adults.

In addition, comparative studies performed in three other areas in Zaire with varying degrees of mild iodine deficiency but with no endemic goiter and no impairment of thyroid function in the adult fraction of the populations also showed that the serum TSH level was elevated in the newborns (19).

These data clearly indicate that newborns are the target population regarding the action of goitrogenic factors in the environment, and that consequently systematic neonatal screening for congenital hypothyroidism constitutes the most sensitive index for detecting impairment of thyroid function resulting from environmental goitrogenic factors in a given population.

**Mild Iodine Deficiency**

It is often considered that iodine deficiency is a problem of remote areas in developing countries and is of no relevance for western countries. On the contrary, the introduction of systematic neonatal screening for congenital hypothyroidism in western countries for the last 10 years has clearly shown that even in Europe today there are still several areas in which borderline iodine deficiency has clear-cut effects on thyroid function of newborns and young infants and where, consequently, iodine deficiency still constitutes a public health problem which should be studied and corrected, particularly in young infants (21).

The potential importance of these observations is that an adequate supply of thyroid hormones is required precisely during early life for normal development of the brain. The possibility arises that transient impairment of thyroid function in the newborn in western countries, particularly in preterm infants, could play a significant role in the various types of neurointellectual deficiencies frequently observed in the long-term follow-up of preterm infants (22).
Our group in Brussels has described a new syndrome called "transient primary hypothyroidism of the newborn" (21,23). This syndrome is characterized by three main features: (a) It is observed principally in preterm infants with acute pathological conditions such as severe infections. (b) The biochemical picture of hypothyroidism develops only after birth, whereas in permanent sporadic congenital hypothyroidism this picture is already present at birth. (c) Hypothyroidism is only transient, as it corrects within a couple of days or weeks, either spontaneously or after a short period of substitutive therapy with thyroid hormones. The incidence of the syndrome of transient primary hypothyroidism of the newborn was as high as 1 in 600 live births in Brussels; that is an incidence six times higher than the incidence of permanent sporadic congenital hypothyroidism.

This observation prompted us to perform in Brussels a systematic study of thyroid function during early infancy as a function of gestational age at birth (24). We studied 103 unselected newborns admitted to our neonatal unit over a period of 6 months. The patients were divided into four groups on the basis of gestational age at birth. Group A were full-term infants, and groups B, C, and D were preterm infants of decreasing gestational age. We determined the serum concentration of TSH, T4, and T3, and performed TRH tests: Serum TSH and T3 were determined before and 30, 60, 90, and 120 min after the intravenous injection of 40 μg TRH. The integrated area under the TSH response curve was used as an index of TSH secretion, and the peak T3 after TRH injection was used as an index of the responsiveness of the thyroid to acute TSH hyperstimulation. The tests were performed on day 5 and repeated weekly up to the end of the follow-up period at the age of 11 weeks.

The results obtained on day 5 showed that from group A, through groups B and C, to group D, i.e., from full term to preterm, the basal TSH and TSH secretory areas markedly increased. Conversely, total and free T4, total T3, and peak T3 after TRH progressively decreased. These results indicate a decreasing functional capacity of the thyroid gland with the degree of prematurity.

During the following days, 11 of the 103 infants developed overt biochemical signs of primary hypothyroidism with an increasing frequency from full term to small preterm infants. In the 92 other infants, basal TSH and TSH secretion on day 5 were still significantly higher in small preterm than in full-term infants, and total and free T4, basal T3, and peak T3 after TRH were lower in the first group than in the second one. The differences between the groups progressively decreased with age and disappeared at about 5 to 6 weeks of age.

This work indicates that, compared to full-term infants, preterm infants in Belgium have a higher risk of developing transient primary hypothyroidism, and that this risk decreases with time.

Belgium is known to be an area with a rather low iodine supply (23). Consequently, the possibility arises that the metabolic situation observed in preterm infants in Belgium could be critically influenced by a state of moderate iodine deficiency. This interpretation is supported by the observation that in Denmark, for example, where the iodine supply is high, preterm infants have low TSH
responses to TRH (25), whereas in Central Germany, where the iodine supply is still lower than in Brussels, transient primary hypothyroidism with markedly elevated basal TSH and goiter is frequently observed even in healthy full-term infants (26).

SUMMARY AND CONCLUSIONS

The public health consequences of iodine deficiency in the world are much more important than what is usually considered. Many areas in developing countries are affected by endemic goiter and endemic cretinism resulting from severe iodine deficiency. In these areas the newborns constitute a target population for the antithyroid action of goitrogenic factors in the environment. Theoretically, correction of iodine deficiency is easy, and endemic goiter is one of the conditions resulting from a deficiency of trace elements which should have been eradicated. In reality, this has not been the case because of major socioeconomic and technical limitations in the introduction, implementation, and organization of prophylactic programs in the affected areas.

Even in western countries with moderate iodine deficiency there is clear-cut impairment of thyroid function in the newborn population, particularly in preterm infants. Consequently, there is an urgent need, even in western countries, to carefully determine the iodine requirement of newborns, particularly that of preterm infants, and the factors involved in their hypersensitivity to iodine deficiency.

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DISCUSSION

Dr. Dorner: Did you measure urinary iodine output in this Zaire region? Would you please interpret your thiocyanate values? Concerning the supplementation of pregnant women, I would be interested to know which chemical form you prefer and at what dose. Is it possible to increase iodine intake sufficiently by seafood alone instead of iodinated salt?

Dr. Delange: The mean daily urinary excretion of iodine in the endemic area measured in 276 normal adults was 15 µg/day, which is about 10% of the normal value, i.e., 150 µg/day. This is still lower than in southern Germany.

Regarding iodine supplementation of pregnant women, my answer would be as follows: In isolated areas with extremely severe iodine deficiency such as Zaire and Nepal, we have organized mass programs of iodine prophylaxis by injecting the whole population, including the pregnant women, with large doses of slowly resorbable iodized oil. Such programs are not recommended in western countries because the degree of iodine deficiency is not severe enough. The necessity to supplement pregnant women with iodine in Europe should be investigated. Sea fish contain a lot of iodine and are recommended to pregnant women. The fish should be grilled and not boiled because the iodine escapes in the boiling water.
Dr. Chandra: What is the role of iodine in immune responses? We found that the only aspect of immunity which seemed to be affected by iodine deficiency was polymorphonuclear leukocyte function, especially its capacity to kill ingested bacteria and fungi. In patients with hypothyroidism either of endemic or unknown origin, the bacterial capacity of neutrophils was reduced and was corrected by giving appropriate replacement therapy with thyroxine; this may be related to the role of iodine in intracellular metabolism. I have two questions. First, why do only about 40 to 60% of people in the severely affected endemic areas develop symptoms of either goiter or hypothyroidism? What determines whether a person will develop myxedema or neurological symptoms? Second, how well does thyroid hormone transfer from the mother to the baby? If I recollect correctly, trials in Papua, New Guinea showed that the administration of iodized oil did not prevent neonatal hypothyroidism in the endemic areas there.

Dr. Delange: Thank you for your comment on the relationship between iodine and immunity. The reason(s) why only part of a population submitted to a uniform iodine deficiency would develop goiter is unknown. There is a family aggregation, which does not imply that there is a genetic defect behind it. The possible additional role of autoimmune processes has been ruled out.

Regarding the etiopathogenesis of endemic cretinism, this is a long story; the myxedematous cretins seen in Zaire resulted from severe thyroid failure that occurred during fetal and early postnatal life. The pathogenesis of neurological cretinism is unclear. The direct role of iodine deficiency on brain development has been proposed but not conclusively demonstrated.

Regarding iodine prophylaxis during pregnancy, it has been shown in Zaire, New Guinea, Ecuador, and several other areas that correction of iodine deficiency during pregnancy would indeed prevent the occurrence of endemic cretinism, either the neurological or the myxedematous types. Iodide crosses the placenta; thyroid hormones do not.

Dr. Picciano: I was very interested in your comment that iodine intake of the breast-fed infant is low. I am surprised that it is low because iodine is unique among trace elements in that the mammary gland actively sequesters it. In fact, there is a recent case report of iodine toxicity in a breast-fed infant. The nursing mother was using an iodine-containing douche which resulted in very high levels of iodine in the milk. Likewise, there are some old reports indicating that once iodization of salt had been instituted the iodine content of human milk had doubled. Actually, I have not seen any modern data on the iodine content of human milk, but I suspect that in the United States it is much higher than literature values suggest because of the mechanism by which the mammary gland actively sequesters iodine. Do you have any data on human milk iodine content in modern times in Europe?

Dr. Delange: We do have data. You are right in saying that the mammary gland shares with the thyroid gland, the parotid glands, and the stomach the capacity to actively concentrate iodide. Conversely, thiocyanate impairs the trapping of iodide by the mammary gland. In Zaire, where the iodine supply of lactating mothers is low and where iodine deficiency is aggravated by a state of thiocyanate overload resulting from the consumption of poorly detoxified cassava, the mean iodine content of human milk is about 2 μg/dl. It is 12 μg/dl in Brussels.

Dr. Eggermont: In recent years we have also been interested in the study of neonatal thyroid metabolism. First, we observed a myxedematous newborn with high serum TSH from a mother regularly consuming tea from sea plants during pregnancy. Secondly, we have been faced with a preterm adapted formula containing 10 times more iodine than the usual preparations, i.e., 150 to 200 μg/dl. A number of preterm infants of fetal age below 34
weeks fed the iodine-rich formula developed transitory hypothyroidism; all had increased serum TSH. Thirdly, a prospective study of thyroid metabolism in healthy and sick preterm infants of 31 weeks fetal age has been undertaken. In the sick preterm infants serum TSH was similar to that in the control group, but serum T₄ and T₃ were well below the control values (Helv Paediatr Acta, 1984;39:209–22). Hence my question to Dr. Delange: What is the reason for seeing, in the absence of excess iodine, normal TSH values in preterm infants in Leuven and high TSH values in those in Brussels?

Dr. Delange: You are perfectly right to once more underline the potential danger of iodine excess in newborns. I would like to comment on the reasons why a young infant would be much more sensitive than a child or an adult to the toxic effect of iodide. Iodide blocks the synthesis and secretion of thyroid hormones in the thyroid when the iodide in the thyroid gland reaches a critical level per unit weight. There are three factors which make a newborn more sensitive: (a) his trapping of iodine is extremely high; (b) the gland is very small and consequently you rapidly reach a high iodine concentration per unit weight; and (c) he lacks the autoregulation mechanism present in children and adults which determines that, from a certain iodine supply on, the thyroid gland will automatically block the trapping and increase the release of iodide. Regarding the question about why in Brussels so many premature infants would have elevated TSH with low T₄, which by definition is hypothyroidism, and why this does not occur in Leuven, 30 km away—I do not know. It might be that the iodine supply in the two places is slightly different. However, what we observe in most places in the world is that premature infants have low T₄, low T₃, but normal TSH and normal TRH tests.

Dr. Mertz: I have two brief questions. First, do you know of any influence of moderate iodine deficiency, not cretinism, and of moderate hypothyroidism on intellectual development? Second, in the United States we can calculate that if we consume the right combination of foods, our daily intake can easily go up to 600 μg. Where would you draw the limit on intakes that should not be exceeded?

Dr. Delange: We have no data on the possible long-term damage resulting from transient neonatal hypothyroidism in preterm infants. The reason is that the methodology is incredibly difficult. Regarding the iodine supply in the United States, the recommended iodine intake is about 150 μg/day in adults. It is true that in some parts of the United States the iodine supply is much higher than that. A recent report indicates an increase in the prevalence of goiter in schoolchildren in areas with such high iodine supply and suggests the possible role of iodine excess (Trowbridge et al. Pediatrics 1975;56:82). I think that based on the evidence, including epidemiological data and metabolic studies, the lower limit is certainly between 50 and 70 μg/day and the upper limit is most probably not higher than 600 μg/day. That is the range in which I would not see major problems.