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Iodine intake as a determinant of thyroid disorders in populations

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Depending on the availability of iodine, the thyroid gland is able to enhance or limit the use of iodine for thyroid hormone production. When compensation fails, as in severely iodine-deficient populations, hypothyroidism and developmental brain damage will be the dominating disorders. This is, out of all comparison, the most serious association between disease and the level of iodine intake in a population.

In less severe iodine deficiency, the normal thyroid gland is able to adapt and keep thyroid hormone production within the normal range. However, the prolonged thyroid hyperactivity associated with such adaptation leads to thyroid growth, and during follicular cell proliferation there is a tendency to mutations leading to multifocal autonomous growth and function.

In populations with mild and moderate iodine deficiency, such multifocal autonomous thyroid function is a common cause of hyperthyroidism in elderly people, and the prevalence of thyroid enlargement and nodularity is high. The average serum TSH tends

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to decrease with age in such populations caused by the high frequency of autonomous thyroid hormone production.
On the other hand, epidemiological studies have shown that hypothyroidism is more prevalent in populations with a high iodine intake. Probably, this is also a complication to thyroid adaptation to iodine intake. Many thyroid processes are inhibited when iodine intake becomes high, and the frequency of apoptosis of follicular cells becomes higher. Abnormal inhibition of thyroid function by high levels of iodine is especially common in people affected by thyroid autoimmunity (Hashimoto's thyroiditis).
In populations with high iodine intake, the average serum thyroid-stimulating hormone (TSH) tends to increase with age. This phenomenon is especially pronounced in Caucasian populations with a genetically determined high tendency to thyroid autoimmunity. A small tendency to higher serum TSH may be observed already when iodine intake is brought from mildly deficient to adequate, but there is at present no evidence that slightly elevated serum TSH in elderly people leads to an increase in morbidity and mortality.
Conclusion: Even minor differences in iodine intake between populations are associated with differences in the occurrence of thyroid disorders. Both iodine intake levels below and above the recommended interval are associated with an increase in the risk of disease in the population. Optimally, iodine intake of a population should be kept within a relatively narrow interval where iodine deficiency disorders are prevented, but not higher. Monitoring and adjusting of iodine intake in a population is an important part of preventive medicine.

Iodine is relatively abundant in the aquatic environment of the earth, the sea, but scarce in most parts of the terrestrial environment. To compensate for the low amount of iodine available for thyroid hormone production, a series of mechanisms have developed in human and other mammals.

When the supply of iodine is below a certain limit, autoregulatory intrathyroidal mechanisms enhance the activity of the many processes involved in the use of iodine for production of thyroid hormones.[1] If this adaptation is not sufficient to keep thyroid hormone production normal, a further enhancement of thyroid activity will take place through hypothalamic/pituitary feedback, leading to an increase in the synthesis and secretion of thyroid-stimulating hormone (TSH). Moreover, there are other mechanisms both inside the thyroid and in the peripheral tissues that tend to stabilise the production of active thyroid hormone.[2] Assisted by such mechanisms, even small supplies of iodine will be sufficient to keep the thyroid function at a level allowing reproduction and other activities necessary for the survival of the species.

However, the reproduction and survival may be impaired not only by insufficient thyroid hormone production caused by iodine deficiency, but also by excessive thyroid hormone production, leading to thyrotoxicosis. If all thyroid processes involved in use of iodide are up-regulated to compensate for iodine deficiency and the individual then suddenly is exposed to iodine excess, for example, from eating seaweed, then the individual is prone to develop hyperthyroidism. Fortunately, the thyroid also harbours mechanisms that almost immediately detect iodine excess and subsequently down-regulate the processes involved in thyroid hormone synthesis and secretion[3] to protect against hyperthyroidism.

Thus, the thyroid gland contains an advanced set of processes that may enhance or block the use of iodine for thyroid hormone production. A likely cause for many thyroid disorders is some degree of complication to this complexity of processes. Because the processes activated during low and high iodine intakes are different, the type of disease that dominates thyroid pathology in populations may be different depending on the level of iodine intake.

In an individual member of society, the risk of a certain thyroid disease will depend on the level of iodine intake and on fluctuations in iodine intake. Moreover, the risk of a number of thyroid diseases will depend on the interaction between iodine intake and genetics of the individual as well as exposure to other environmental factors.[4]

The spectrum of diseases caused by iodine deficiency and iodine excess

The classical understanding of the relationship between iodine intake and disease was that people would develop disease if their iodine intake were below a certain limit.[5] Because natural foods and beverages contained little iodine in many parts of the world, many populations were affected by iodine deficiency disorders.[6] On the other hand, even intake of relatively large amounts of iodine were considered well tolerated, with toxicity seen only if intakes were many-fold higher than the recommended intake necessary for normal thyroid hormone production.[7] Until relatively recently, the only population in the world in which excessive intake of iodine had been described as a main cause of disease lived in some costal areas of the Japanese island Hokkaido.[8] The excessive iodine intake in this population was attributed to the daily use of iodine-rich seaweed for consumption.

The development of thyroid disease investigation from case identification into various types of population studies has revealed a much more complex and subtle relation between iodine intake and the occurrence of thyroid disease. It is now clear that even relatively small differences in the level of iodine intake between otherwise comparable populations are associated with considerable differences in the epidemiology of thyroid disease. Many studies now indicate that even a small change in the level of iodine intake of a population will lead to a reduced frequency of some thyroid disorders, but that other types of disease will become more common.[9]

It is important to realise that the association between iodine intake of a population and the occurrence of thyroid disorders in the population is U-shaped[10] There is a relatively narrow interval of optimal intake, and more disease will develop in the population with intakes both lower and higher than this interval. Identification of the optimal level of intake and studies of the methods to obtain and maintain such a level of iodine intake in the population are important for prevention of thyroid disorders.

Brain damage from low iodine intake

Table 1 illustrates the spectrum of disorders that somehow depends on the iodine intake level of the population.

Table 1
Increase in risk of disease in the population associated with population iodine intake outside the optimal level.

Iodine nutrition	Median urinary iodide concentration μg/L	Disease
Severe ID	<25	Cretinism Goitre Hypothyroidism
Moderate ID	25–50	Low IQ Goitre Hypothyroidism Hyperthyroidism
Mild ID	50–100	Goitre Hyperthyroidism
Optimal	100–200	
More than adequate	200–300	Hypothyroidism Early Graves' disease?
Excessive	>300	Hypothyroidism Goitre Early Graves' disease?

The exact boundaries of iodine intake associated with the different diseases depends on intake of goitrogens and other nutritional deficiencies. Subgroups of the population may have iodine intake levels that differ from the main population.

By far, the most serious defect that may be associated with abnormal iodine intake is developmental brain damage caused by severe iodine deficiency.[11] In foetal life, brain development takes place over a long period, starting as early as a few weeks after conception and continuing during the first years after birth.[12]

The iodine necessary for thyroid hormone production by the mother, the foetus and the neonate/child during the period of breast-feeding has to be in the diet of the mother. Unfortunately, iodine utilisation is not that efficient in pregnant women probably caused by the increase in renal glomerular filtration rate.[13] For the same concentration of inorganic iodide in plasma, this will lead to a higher urinary iodide excretion. Conversely, for the same urinary iodide excretion, the plasma inorganic iodide concentration will be lower. Thus, the need of iodine to keep thyroid function normal is higher in pregnancy than in the normal state, also because of the increase in maternal thyroid hormone secretion associated with pregnancy and the accumulation of iodine in the foetus.[14] This is the background for the recommendation of the WHO/UNICEF/ICCIDD of a higher-than-usual iodine intake during pregnancy.[15]

A number of mechanisms are involved in the increase in thyroid hormone requirement and the compensatory increase in thyroid hormone production in pregnancy. An important mechanism seems to be the increase in peripheral deiodination of thyroid hormones to inactive compounds by the type III iodothyronine deiodinase (D3). The major site of this deiodination appears to be the pregnant uterus and placenta.[16] The process is already active from early pregnancy and, corresponding to this, the serum concentration of reverse T3 is relatively high in early pregnancy.[17] Reverse T3 is a hormonally inactive iodothyronine produced by D3 catalysed deiodination of T4.[18]

Level of iodine intake in pregnant women associated with risk of brain damage

Many studies have shown that severe iodine deficiency is associated with a high frequency of goitre and hypothyroidism in a population, and that frank cretinism and less severe intellectual impairment may be common in such populations[5,11] (Table 1).

The description of iodine deficiency as severe, moderate or mild was based on compilations of data such as illustrated in Fig. 1. It is the association between the frequency of goitre and the level of urinary iodine excretion in various population cohorts in Latin America.[19] In severe iodine deficiency, all subpopulations had a high frequency of goitre; in moderate iodine deficiency, the majority of

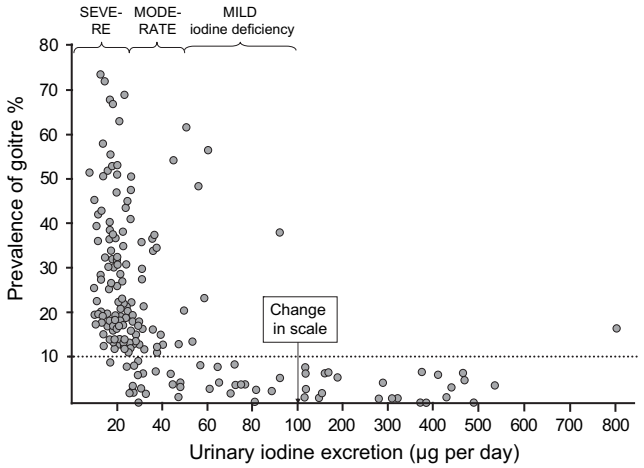

Fig. 1. Average urinary iodine excretion and prevalence of goitre by clinical examination in 186 localities of Central America 1965–1967. In each locality members of around 20 randomly selected families were investigated. A total of 21,611 people from 3,712 families were investigated for goitre, and iodine and creatinine were measured in late morning spot urine in a random sample of 3,181 participants. Daily iodine excretion was estimated from iodine and creatinine concentrations using an equation correcting for body weight, age and sex depending differences in 24 hour urinary creatinine excretion.[20] Data from Ascoli and Arroyave.[19]

subpopulations had a high frequency of goitre; and in mild iodine deficiency, some subpopulations suffered from goitre (Fig. 1). The reasons for the disparity in goitre frequency with apparently identical iodine intakes may be several. The risk of goitre development caused by iodine deficiency may depend on genes[21,22], and on deficiency of other nutrients[23] or intake of goitrogens.[24,25] Moreover, iodine intake of some populations may show seasonal variation.[26]

The level of iodine deficiency at which there may be risk of intellectual impairment is not fully established. Brain damage is not directly caused by lack of iodine, but indirectly due to insufficient synthesis of thyroid hormones by the pregnant woman, the foetus and the infant. Thus, the risk would depend not only on the level of iodine supply (and the susceptibility of the brain to such damage), but also on the capability of the thyroid of the mother and child to synthesise hormone at a given level of iodine intake. As discussed above, deficiency of other nutrients and intake of goitrogens that interfere with enzymes or transporters used in the process of thyroid hormone synthesis may worsen the effects of low iodine intake. One such goitrogen is thiocyanate that may be in the diet or generated in the liver from cyanide in tobacco smoke.[27] Low intake of iron[23] and other essential nutrients[24] may worsen the effect of iodine deficiency. In addition, it is important to recognise that a certain average level of iodine intake of a population covers a large spread in iodine intake of the individual members of society. For example, in populations where iodine in milk and other dairy products are a major source of iodine nutrition, individuals who avoid such products may have a much lower iodine intake than suggested by the population median iodine intake[28] and quite different levels of iodine intake may be seen in populations with different cultural backgrounds.[29]

In recent years, several studies have suggested that even in areas where iodine deficiency is only moderate, as judged from median urinary iodine excretion, there may be a risk of impaired intellectual development.[30,31]

The shift from excess hypothyroidism to excess hyperthyroidism associated with iodine deficiency

Severe iodine deficiency may cause excessive hypothyroidism in a population because of lack of substrate for thyroid hormone production. However, mild-to-moderate iodine deficiency is not associated with hypothyroidism. On the contrary, it is associated with excess hyperthyroidism in the population.[32] Apparently, at moderately low levels of iodine intake, the thyroid gland is able to compensate for this and keep thyroid hormone production normal. However, as discussed below, the price of prolonged thyroid hyperactivity to exploit limited iodine supply is a tendency to develop autonomous growth and function of clusters of follicular cells.

Figure 2 shows the occurrence of different subtypes of hyperthyroidism in a comparative study of thyrotoxicosis epidemiology in East Jutland, Denmark, with long-standing mild-to-moderate iodine deficiency and in Iceland with long-standing relatively high iodine intake.[33] In Iceland, nearly all patients had thyrotoxicosis caused by Graves' disease. Graves' disease was also common in East Jutland, but it tended to develop later in life. The lifetime risk of developing Graves' hyperthyroidism did not differ between East Jutland and Iceland, but the incidence of multinodular toxic goitre was much higher in East Jutland. This difference in disease pattern led to a much different association between age and the development of thyrotoxicosis in the two areas. In Iceland, hyperthyroidism was mainly observed in young and middle-aged people, whereas it was much more common in the old when iodine intake was low.[33] A high incidence of hyperthyroidism from multifocal autonomous thyroid function has also been reported from other areas with mild-to-moderate iodine deficiency.[34,35]

Multinodular toxic goitre is a complication to non-toxic simple goitre. It has been speculated that the frequent development of goitre in people living with mild or moderate iodine deficiency might be secondary to elevated serum TSH caused by lack of iodine for thyroid hormone production.[36] However, average serum TSH has never been found elevated in adult populations with mild-to-moderate iodine deficiency. On the contrary, TSH tends to be low in such populations.[37,38] This is illustrated in Fig. 3, showing the gradually lower average serum TSH with age in two Danish population cohorts with mild and moderate iodine deficiency. In the study depicted in Fig. 3, all participants had a careful ultrasonographical investigation of the thyroid gland. If participants with any type of irregular/nodular thyroid structure were excluded from the study, there was no decrease in serum TSH with age.[39]

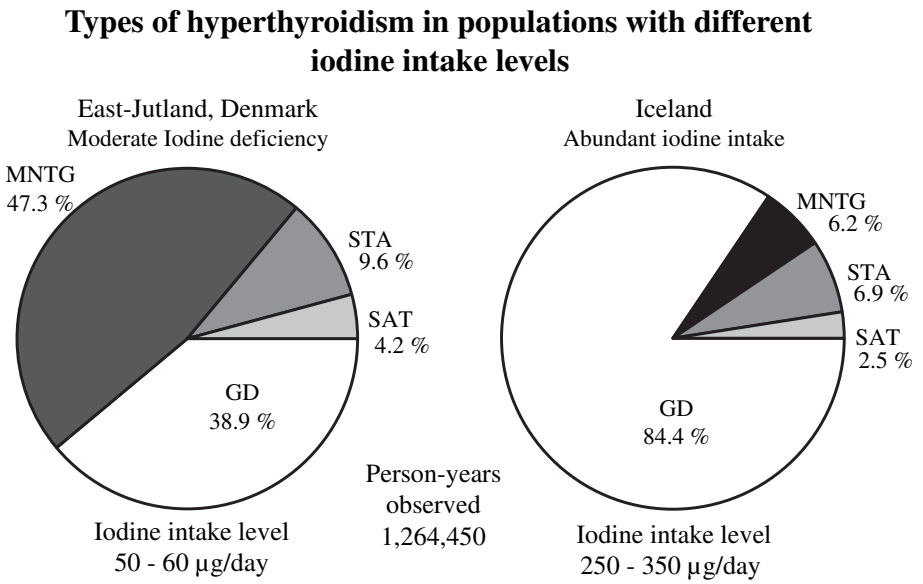

Fig. 2. Nosological types of hyperthyroidism with different iodine intake levels. Relative frequency of the four most common nosological types of hyperthyroidism in Iceland, with relatively high iodine intake from consumption of fish and high iodine content of dairy products, and from East Jutland, Denmark, with mild-to-moderate iodine deficiency. MNTG, multinodular toxic goiter; GD, Graves' disease; STA, solitary toxic thyroid adenoma; SAT, subacute thyroiditis. Data from Laurberg et al.[33]

Similar findings of a relatively low serum TSH in a population with mild-to-moderate iodine deficiency have been reported by Völzke et al.[40] from Northeast Germany.

The mechanism by which a low iodine supply leads to thyroid autonomy is only partly understood.[41] Low iodine intake leads to up-regulation of many thyroidal processes that may lead to growth of the gland. Another important factor may be the up-regulation of the thyroidal production of H_2O_2 to facilitate thyroid hormone production.[42,43] H_2O_2 excess may promote mutations of thyroid cells, and thereby be involved in the development of clusters of autonomous functioning follicular cells.

Corresponding to the high incidence of multinodular toxic goitre in elderly subjects in moderate iodine-deficiency areas and the relatively low average serum TSH, the prevalence of subclinical

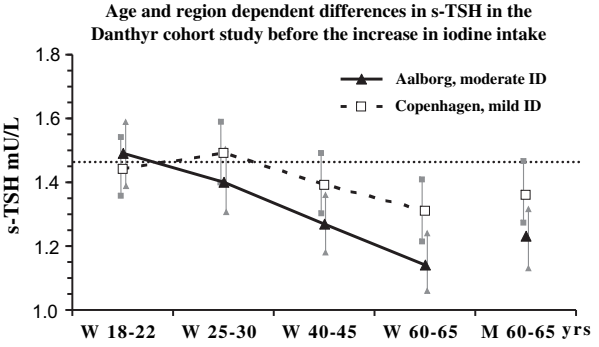

Fig. 3. Age and region-dependent differences in s-TSH in the DanThyr cohort study before the increase in iodine intake in Denmark. Mean serum thyrotropin (TSH) after logarithmic transformation and 95% confidence intervals for the mean in 4,356 participants of the DanThyr C1a population study. The calculation was based on participants who had not been treated for thyroid disorders. The Copenhagen area had mild iodine deficiency with median urinary iodine excretion in subjects not taking iodine supplements of 61 µg/l. The Aalborg area was moderately iodine-deficient (urinary iodine 45 µg/l). In each area the study included four groups of women (W) and one group of men (M) within the age intervals indicated. Data from Knudsen et al.[39]

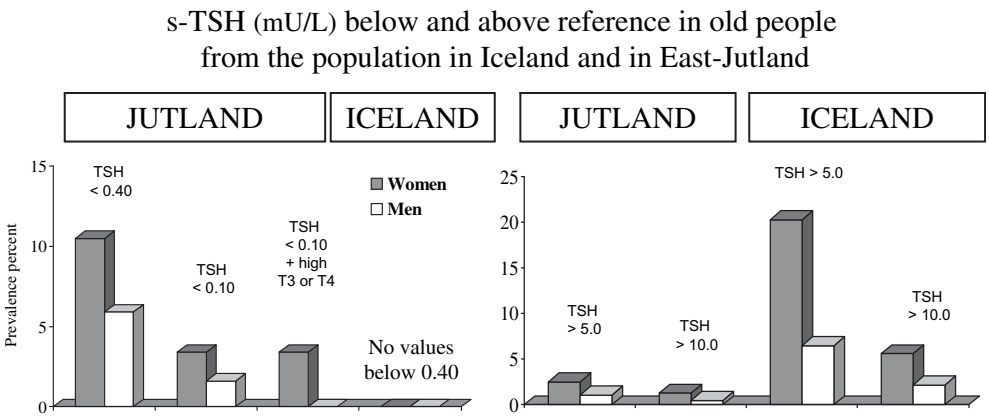

Fig. 4. Prevalence rates of thyroid hyperfunction with serum TSH below the reference range and thyroid hypofunction with TSH above the TSH reference range (0.4–4.0 m U/l) in 68-year-old people living in Iceland with relatively high iodine intake and in Jutland with moderate iodine deficiency. Data from Laurberg et al.[38]

hyperthyroidism is high in such populations.[38,41] Subclinical hyperthyroidism is a mild hyperthyroidism with low TSH but with T4 and T3 within the normal reference range. In a comparative population study of 68-year-olds from Iceland and East Jutland, Denmark, subclinical hyperthyroidism was much more prevalent in the elderly from Denmark (Fig. 4).

Iodine intake and the prevalence of circulating thyroid autoantibodies

In many people, the thyroid gland is not tolerated well by the immune system, as illustrated by the frequent finding of lymphocytic infiltration of the gland. In autopsy studies of white (Caucasians) and black Americans as well as British white and Japanese, Okayasu et al.[44,45] demonstrated lymphocytic thyroid infiltration in about 40% of white females over 20 years of age and up to 50% in elderly women living in the USA and in the UK. This was around 20% of the white males. In the black Americans and in the Japanese, the occurrence of lymphocytic thyroid infiltration was also common, but the frequency was less than half of that found in Caucasians.

The frequency of detecting thyroid antibodies in blood (thyroid peroxidase antibodies (TPO-Ab) or thyroglobulin antibodies (Tg-Ab)) in population studies is somewhat lower.[46] Apparently, a fraction of the population with lymphocytic infiltration of the thyroid antibodies in serum. Thyroid ultrasonography may show low echogenecity or irregular pattern of such glands. In the DanThyr study, about 50% of people with measurable TPO-Ab had low or irregular echogenecity of the thyroid when measured by ultrasonography.[47]

As discussed below, high iodine intake is associated with more cases of autoimmune thyroid disease, and it might be expected that the prevalence of harbouring circulating thyroid antibodies would be low in populations with a low iodine intake and high in populations with a high iodine intake. However, the association between iodine intake and the presence of circulating thyroid antibodies is considerably more complex.

As discussed previously[46], it is difficult to interpret and compare the many studies where both thyroid antibodies and iodine status have been measured in one or more populations. People with nodular goitre relatively often have circulating thyroid antibodies[48], probably caused by enhanced release of thyroid antigens from the abnormal gland. Thus, circulating thyroid antibodies are common in populations where goitre is common because of iodine deficiency.[49] A sudden increase in iodine intake in an iodine-deficient population may induce enhanced thyroid autoimmunity[50], but this may at least partly be a transient phenomenon.[50,51] It has also been reported that the prevalence of lymphocytic thyroid infiltration becomes high after an increase in population iodine intake.[52]

On the other hand, circulating thyroid antibodies are not extraordinarily common in populations with stable high iodine intake[38,49], but people with thyroid antibodies are at a higher risk of developing thyroid dysfunction when the iodine intake is high.[53]

Hypothyroidism in populations with a high iodine intake

It is well established that individual patients with autoimmune thyroiditis may develop hypothyroidism when exposed to excess iodine.[54] Considering the very frequent occurrence of thyroid autoimmunity in the population, it would be expected that a high iodine intake would be associated with a high frequency of subclinical (with elevated serum TSH but a free T4 estimate within the reference range) and overt (elevated TSH and low estimate of free T4) hypothyroidism, and this has indeed been convincingly demonstrated.[38,55,56]

Figure 4 shows the difference in finding some degree of thyroid hypofunction with elevated serum TSH in Iceland with abundant iodine intake and East Jutland, Denmark, with moderate iodine deficiency. In the study, the influence of the different iodine intakes on the elderly people was so profound that the distribution of serum TSH in the two populations was different.[38] There was a shift of TSH values to the left in low iodine intake Denmark, whereas the TSH distribution was displaced to the right in Iceland with a higher iodine intake.[38]

An interesting question is whether the higher serum TSH associated with a higher iodine intake of the population is entirely related to an increase in serum TSH in people with some degree of thyroid autoimmunity, or whether it is a more general phenomenon related to down-regulation of thyroid function or maybe apoptosis of follicular cells.[57] The results obtained by Li and colleagues[53] in China suggest that the increase in frequency of hypothyroidism after an increase in the level of iodine intake is confined to people with thyroid autoimmunity, but more studies are needed to evaluate this in detail.

On the other hand, many individuals living in high iodine intake areas and having elevated serum TSH have no measurable circulating thyroid antibodies.[38,55] One possible explanation for this apparent discrepancy may be that only part of the people affected by thyroid autoimmunity have measurable circulating thyroid antibodies. As discussed above, the frequency of finding lymphocytic infiltration in the thyroid in autopsy studies[44,45] is considerably higher than the frequency of finding circulating thyroid antibodies in population studies.[49] In a recent study from Brazil[58] (with abundant iodine intake[59]), it was shown that patients with subclinical hypothyroidism and a thyroid ultrasonography examination suggesting autoimmune thyroiditis, but with no measurable thyroid antibodies in serum, had the same risk for development of overt hypothyroidism as patients who were antibody positive. Patients with subclinical hypothyroidism having no antibodies and with a normal pattern by ultrasonography had a much lower risk of progression to overt thyroid insufficiency.

The level of iodine intake at which the occurrence of hypothyroidism begins to increase in a population seems unfortunately to be low, even below the interval of recommended iodine intake.[56] Figure 5 shows the results of a comparative study of incidences of overt thyroid dysfunction in two areas of Denmark with mild (Copenhagen) and moderate (Aalborg) iodine deficiency. The study was performed before the Danish iodine fortification programme. As discussed above, hyperthyroidism is common in populations with mild and moderate iodine deficiency because of a high incidence of multinodular toxic goitre. In accordance with this, the highest incidence value observed in this population study[60] was that of hyperthyroidism in moderately iodine-deficient Aalborg followed by hyperthyroidism in mildly iodine-deficient Copenhagen. Overt hypothyroidism was less common in these iodine-deficient populations, but significantly higher in Copenhagen than in Aalborg (Fig. 5). A detailed study of the nosological type of disease leading to overt hypothyroidism in the two areas revealed that the background for the regional difference was that the standardised incidence rate of primary autoimmune hypothyroidism was 53% higher in mildly iodine-deficient Copenhagen than in moderately iodine-deficient Aalborg.[61]

The exact association between the level of iodine intake in a population and the occurrence of hypothyroidism is at present not clear. There are large differences in the incidence of hypothyroidism between countries.[62] Evidently, even small differences in the levels of iodine intake are important as

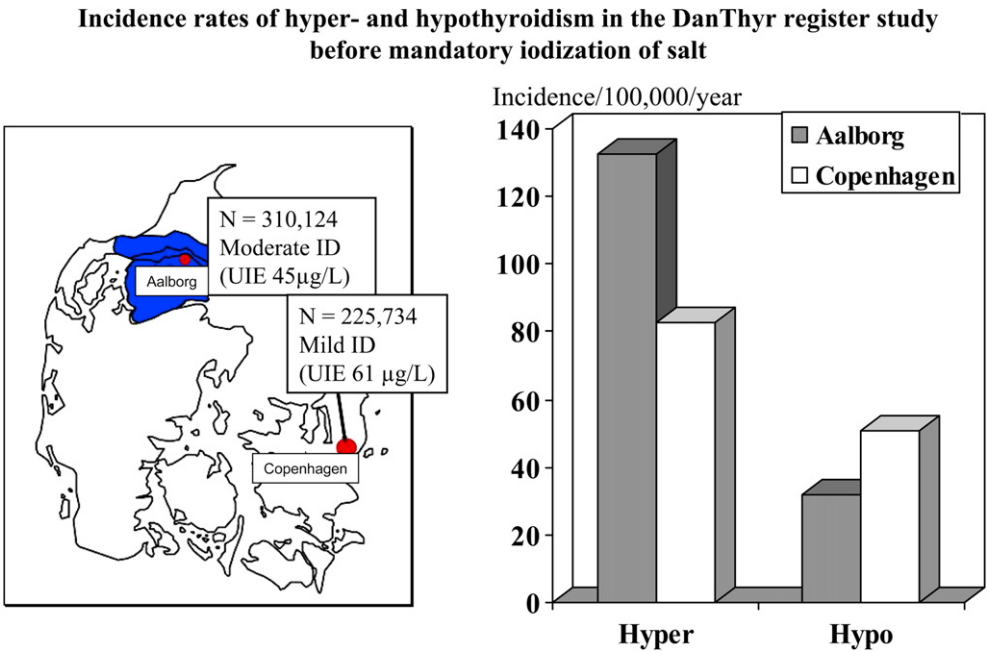

Fig. 5. Incidence rates of overt hyper- and hypothyroidism in the DanThyr Register study, during the time period before mandatory iodization of salt.[60] Two open Danish population cohorts with mild (Copenhagen, median urinary iodine concentration (UIE) 61 µg/l) and moderate (Aalborg, UIE 45 µg/l) iodine deficiency were studied. All new cases of overt hyper- and hypothyroidism were identified during a 3-year period and incidence rates calculated. Hyperthyroidism was statistically significantly more common than hypothyroidism in both areas. Hyperthyroidism was significantly more common in Aalborg than in Copenhagen and hypothyroidism significantly more common in Copenhagen than in Aalborg. Data from Bülow Pedersen et al.[56]

discussed above, but the genetic background of the population also seems to have considerable impact.[62] Caucasian populations are more affected by autoimmune thyroiditis than people with an African genetic background[45] and Japanese[44], and the occurrence of some degree of thyroid hypofunction in elderly individuals is much higher in Caucasians.[63,64]

Recent studies performed in China may suggest that the average serum TSH in a population and the occurrence of hypothyroidism is gradually increasing with the iodine intake level over a wide range.[53,65]

Shifts in the occurrence of thyroid disorders with a change in the iodine intake of the population

It is well documented that programmes directed to increase the iodine intake of iodine-deficient populations will eradicate endemic cretinism and endemic goitre.[66] This is the background for international recommendations on iodine intake and for the many national iodine fortification programmes.

However, the international recommendation is also against an excessive increase in iodine intake of a population, and this should be monitored.[66] This recommendation is based on the finding that an uncontrolled large increase in the iodine intake of a previously iodine-deficient population may be followed by a huge increase in the occurrence of hyperthyroidism and its complications.[67] Two possible mechanisms may be behind this phenomenon. One of them is the 'feeding' of autonomous thyroid nodules with extra substrate for thyroid hormone production. It is well known from many individual cases that a load of iodine from, for example, the use of iodine containing radiographic contrast may lead to a period of hyperthyroidism in individuals harbouring autonomous thyroid tissue.[67] It is very

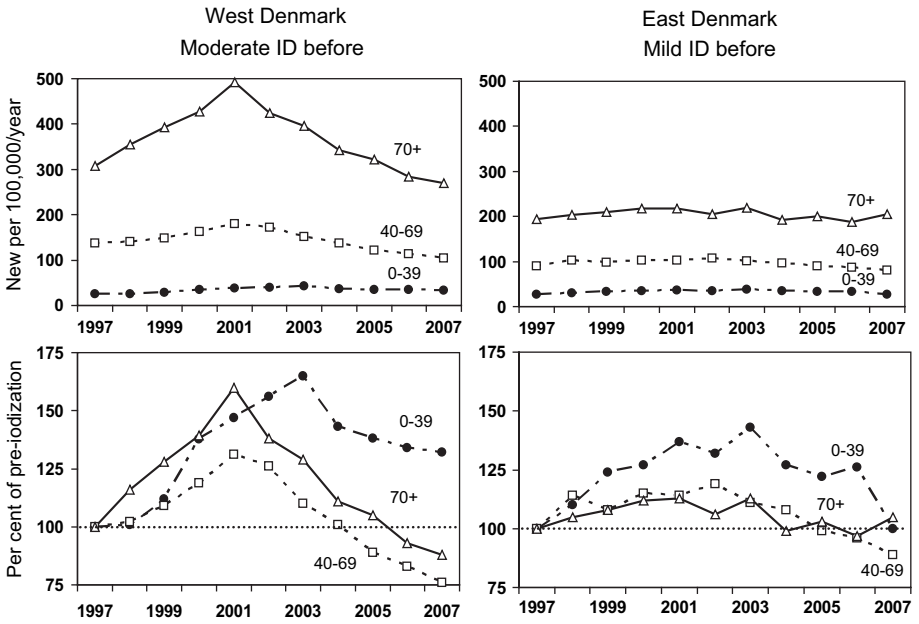

Fig. 6. The incidence rates over time (upper panel) and relative changes in incidence rates (lower panel) of users of anti-thyroid medication in three age groups (0–39, 40–69, 70 + years of age as indicated) in Western Denmark with moderate iodine deficiency (left column) and Eastern Denmark with mild iodine deficiency (right column) before the Danish iodine fortification program.[60] The rates were adjusted to the composition of the population in Denmark in the year 2000. Person years from prevalent users were subtracted. In 1997 there was no iodine fortification of salt in Denmark. *A non-effective voluntary iodization of all salt for consumption (8 ppm) was initiated in 1998, and an effective mandatory iodization of household salt and salt for bread production (13 ppm) was effective from 2001.*[60] *Data from Cerqueira et al.*[73]

common among the elderly in a population with mild and moderate iodine deficiency, as illustrated by the fall in serum TSH with age in such populations (Fig. 3).

Another possible mechanism is the development of hyperthyroidism due to Graves' disease after an increase in iodine intake. Graves' disease appears to be highly dependent on genetic disposition[68], but it may develop earlier[33] (and be more difficult to treat[69]) if the iodine intake is high. It is at present unknown if the appearance of Graves' disease at a younger age when the iodine intake is high is caused by enhancement of the autoimmune abnormality of Graves' disease - or if the mechanism is that low activity. Graves' disease may lead to hyperthyroidism only if there is a certain amount of iodide present as a substrate for thyroid hormone synthesis. Once hyperthyroidism develops, this may by itself worsen the autoimmunity of Graves' disease.[70]

It has been shown that Graves' disease in remission after previous therapy with anti-thyroid drugs is more likely to relapse if the patient is exposed to excess iodine[71], but this gives no indication on the mechanism.

In a Danish monitoring of thyroid disease before and after iodine fortification of salt, special programmes evaluated the development in the incidence of hyperthyroidism. Before the iodisation of salt, the incidence of hyperthyroidism was clearly higher in the moderately iodine-deficient area of Denmark compared with the only mildly iodine-deficient area (Fig. 5).

After salt iodisation, changes in the incidences of hyperthyroidism were monitored in two different ways: one was from prospective identification of all individuals with new biochemical hyperthyroidism in two areas of Denmark with previously mild (Copenhagen) and moderate (Aalborg) iodine deficiency (population cohorts investigated included around 0.5 million people).[72] The other was from identification of people having a new prescription of anti-thyroid drugs in the entire Danish population[73] split into those living in the Western part with average moderate iodine

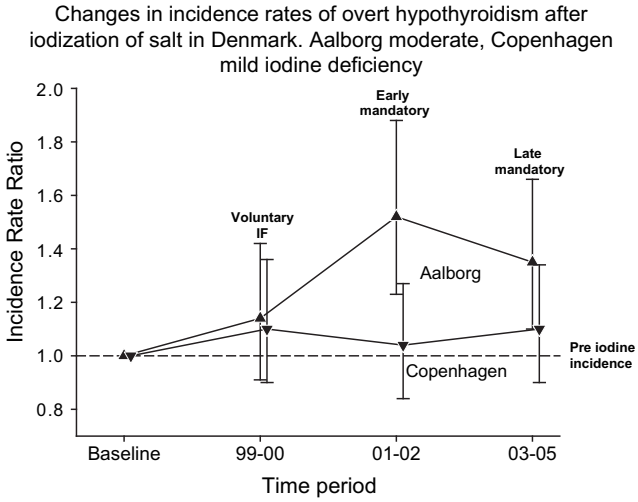

Fig. 7. Incidence rates of overt hypothyroidism before and after iodine fortification of salt in Denmark. The incidence of hypothyroidism in Aalborg with previous moderate ID and Copenhagen with previous mild ID in three periods with different iodine intake compared to baseline, which is the preiodine incidence. New patients with overt hypothyroidism were prospectively identified by linkage to diagnostic laboratory databases and verified by contact to physicians requesting the diagnostic test.[72] The vertical bars indicate the 95% CI to the rate. In Copenhagen the incidence of hypothyroidism was stable. In Aalborg, however, the incidence rates of hypothyroidism were significantly higher in both periods with mandatory ID compared to baseline, as one was not included in the 95% CI. Data from Pedersen et al.[76]

deficiency before the iodisation programme, and those living in Eastern Denmark with only mild iodine deficiency. Both methods have their strengths and limitations, but fortunately, the results have so far been similar.[73,74]

Even if the Danish iodisation programme was very cautious, bringing the median urinary iodine excretion from clearly insufficient to only about the lower limit of the interval recommended by the WHO/UNICEF/ICCIDD[75], an increase in the incidence of hyperthyroidism occurred[73,74], as illustrated in Fig. 6. The majority of people affected had previously been moderately iodine deficient and were elderly. In this group, the increase was transient and it is now back to, or even below, the level before the iodisation programme (Fig. 6). An increase was also observed in young people, although the number of people affected was much lower. In patients below 40 years of age, hyperthyroidism is presumably dominated by Graves' disease. The prescription of anti-thyroid drugs in the young groups is now decreasing again[73], suggesting that the mechanism behind the increase was earlier development of disease. However, it is too early to give a final conclusion.

From the available data on incidences of hypothyroidism in populations with different iodine intakes, it is to be expected that an increase in iodine intake from moderate iodine deficiency to within the recommended range will be associated with some increase in the incidence of overt hypothyroidism. The DanThyr monitoring of overt hypothyroidism in Denmark before and after iodine fortification of salt has shown that a moderate increase occurred in the area with moderate iodine deficiency, whereas no increase was observed in the area with formerly only mild iodine deficiency (Fig. 7).[76]

It is to be expected that the benefits from a decrease in the occurrence of goitre and hyperthyroidism will clearly outweigh the increase in the number of patients with hypothyroidism, but further monitoring is essential. If iodine intake becomes excessive, the number of elderly people with elevated serum TSH may rise. In a recent study of Brazilian women, 23% of white women aged 66–75 years had a serum TSH above 4.0 mU/L[64], similar to our findings in elderly women living in Iceland.[38] Black and mulatto women in Brazil were less affected (11% had TSH >4.0 mU/L) corresponding to the lower prevalence of thyroid autoimmunity in people with this genetic background.[45] In the USA where iodine intake was previously high but is now within the range recommended by the WHO[77],

the prevalence of elevated serum TSH is also considerably higher in elderly white people than in black people.[63]

Fortunately, a moderately high serum TSH in elderly people seems not to be associated with an increase in the risk of disease or death.[78] Similarly, a recent Japanese study suggests that moderately high serum TSH in early pregnancy associated with excessive iodine intake is not associated with adverse pregnancy outcome.[79] However, more studies are needed on the consequences of iodine-induced moderately high serum TSH on the health of a population.

Iodine memory?

One pertinent question when evaluating the association between current iodine intake and the epidemiology of disease in a population is to what degree a previous exposure to a different level of iodine intake (low or high) may have influenced the current occurrences of diseases. For example, brain damage caused by iodine deficiency in early life is not reversible, even if the iodine intake becomes normal.

An increase from low to normal iodine intake is associated with a reduction in thyroid size in the population within a few years.[80] On the other hand, the prevalence of thyroid nodularity is unaltered.[80] This is compatible with the more or less irreversible nature of the abnormalities leading to thyroid nodularity in iodine deficiency.[41]

It remains to be elucidated if the high frequency of hypothyroidism in areas with excessive iodine intake is a reversible phenomenon. Studies of hypothyroid patients living in Japan and Korea with high iodine intake have indicated that a reduction in iodine intake may normalise thyroid function in some of these patients.[81,82] More studies are needed on the association between iodine intake and hypothyroidism in the population and the mechanisms involved.

Conclusion

Both low and high levels of iodine intake associate with an increase in the risk of disease in a population. Optimally, iodine intake of a population should be kept within a relatively narrow interval where iodine deficiency disorders are prevented, but not higher.

Practice points

- The primary priority in iodine nutrition is to avoid severe iodine deficiency with insufficient thyroid hormone production and to prevent developmental brain damage.
- Developmental risk is also present in moderate iodine deficiency.
- Prevention may involve giving iodine supplements to individual pregnant women living in iodine-deficient areas, but otherwise iodine nutrition should be regulated by universal public programmes.
- The optimal level of iodine intake to prevent disease is within a relatively narrow range around the recommended intake.
- Population iodine intake below this level is associated with a high incidence and prevalence of goitre and hyperthyroidism caused by thyroid autonomy. The occurrence increase with age.
- Population iodine intake above this level is associated with a higher level of serum TSH and more cases of hypothyroidism in the population. This affects especially people with some degree of thyroid autoimmunity leading to Hashimoto's thyroiditis.
- People with a Caucasian genetic background have a high tendency to such thyroid autoimmunity, which may affect up to half of elderly women.
- Monitoring and adjusting iodine intake of a population is an important part of preventive health care.

Research agenda

- The many unknown factors involved in iodine regulation of thyroid function should be characterised in detail.
- Studies are needed to define more precisely the limits where iodine deficiency and iodine excess lead an increase in risk of disease in the population.
- Methods to achieve iodine intake within the recommended level for (nearly) every individual in the population should be studied. They may vary between populations.
- The importance of periodic low and excessive iodine intake for later disease needs clarification.

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