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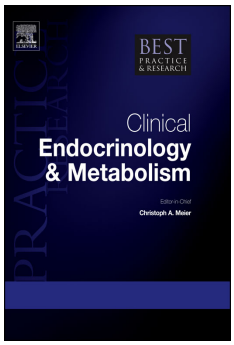

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Emilio Fiore , Massimo Tonacchera , Paolo Vitti

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Influence of iodization programmes on the epidemiology of nodular goitre

Emilio Fiore, Massimo Tonacchera and Paolo Vitti

Department of Clinical and Experimental Medicine, Section of Endocrinology, University of Pisa, Pisa, Italy.

E-mail address of authors

Emilio Fiore**: e.fiore@ao-pisa.toscana.it**

Massimo Tonacchera**: mtonacchera@hotmail.com**

Paolo Vitti**: paolo.vitti@med.unipi.it**

Telephone number. +39 (0)50 995001

Fax : +39 (0) 50 578772

Corresponding author: Paolo Vitti, Endocrinology Unit, University Hospital, University of Pisa, Via Paradisa 2, 56124, Pisa, Italy

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Abstract

Iodine is essential for the synthesis of thyroid hormones. Iodine deficiency can affect human health in different ways, and is commonly referred to as iodine deficiency disorders (IDD). These range from defective development of the central nervous system during the fetal–neonatal life, to goitre in the adult. Only a few countries were completely iodine sufficient before 1990. Since then, a major effort has been made to introduce salt iodization to ensure sufficient intake of iodine in deficient areas. Iodine prophylaxis has been shown to exert a pivotal role in abating goitre and other iodine-deficiency disorders, and has also been shown to modulate the pattern of thyroid diseases. An increased frequency of thyroid autoimmunity and of hypothyroidism has been observed after introducing iodization programmes. Nevertheless, available evidence clearly confirms that the benefits of correcting iodine deficiency, consisting mainly of reducing nodular goitre and non-autoimmune hyperthyroidism, far outweigh the risks of iodine supplementation.

Key words: iodine deficiency, iodine prophylaxis, goiter.

Introduction

Iodine is essential for the synthesis of thyroid hormones. Iodine deficiency has multiple adverse effects. Iodine intake is insufficient in more than 2 billion people, and therefore deficiency of iodine intake is high on the public health agenda worldwide. The term iodine deficiency disorders (IDD) refers to the effect of iodine deficiency in individuals. The clinical consequences of iodine deficiency include goitre, which is the most common clinical manifestation, and cerebral impairment, ranging from mild cognitive defects to cretinism. The frequency and severity of the clinical manifestations are proportional to the magnitude of iodine deficiency (1-5). When severe iodine deficiency occurs during pregnancy, it is associated with cretinism and increased neonatal and infant mortality. Iodine deficiency remains a major global threat to health and development, and is the most common cause of preventable mental impairment worldwide (6-9).

Iodine metabolism

Alimentary iodine is absorbed by the gut and is actively concentrated by the thyroid gland. The body of an adult contains about 20 mg of iodine, and the thyroid concentrates 70–80% of the total iodine content through the sodium–iodine symporter (NIS) located on the basolateral surface of thyrocytes. A normal adult uses about 80 mg/day of iodide to produce thyroid hormones. Ninety per cent of the plasma iodine is excreted by the kidney, and only a small amount in the faeces.

Iodine requirement changes with age and in relation to various physiological conditions (7). According to the World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD), the recommended nutrient intake of iodine is 90 mcg/day in infants and children under 6 years of age, 120 mcg/ day in children 6–12 years of age, and 150 mcg/day in adults. During pregnancy, the recommended intake increases to 250 mcg/day. The recommended intake in lactating women is 250 mcg/ day to compensate for the iodine loss in breast milk.

When iodine intake is slightly insufficient (i.e. < 100 mcg/day), thyroid stimulating hormone (TSH) induces a higher NIS expression, with an increase of thyroid iodine uptake and preferential synthesis of T3, thus allowing a normal content of intrathyroidal iodine. In chronic iodine deficiency, the thyroid content of iodine progressively decreases, the metabolic balance of iodine becomes negative, and goitre ensues (8;10;11).

Patogenesis of goitre and iodine nutrition

Nodular goitre is probably a lifelong condition that starts in adolescence or at puberty. Minimal diffuse enlargement of the thyroid gland is found in many teenage boys and girls, and is almost a physiologic response

to the complex structural and hormonal changes occurring at this time. It usually regresses but, occasionally, (much more commonly in girls) it persists and undergoes further growth during pregnancy (12;13).

Marine (14) first developed the concept, that the thyroid first goes through a period of hyperplasia in response to iodide deficiency as a consequence of the resulting TSH stimulation (15). Eventually, the thyroid enters a resting phase characterized by colloid storage. This is possibly as a result of iodide repletion or a decreased requirement for thyroid hormone. The recurrence of these two phases would eventually result in the formation of multinodular goitre (16;17), at least in genetically predisposed individuals (18;19). Over time, functional autonomy may occur (20), with suppression of TSH. Experimental data obtained in rats fed with an iodine-deficient diet, have clarified the natural evolution of the goitre.

Thyroid follicules are functionally heterogeneous, and cell clones differ for their replicative capacity and ability to produce thyroid hormones. The clonal development of follicles with high replication capacity will induce the onset of non-functioning (cold) or hyperfunctioning (hot) nodules, in which the uptake and thyroid hormone synthesis is independent from TSH stimulation. The increase of size and function of hot nodules induces initially a slight enhancement of thyroid hormone production, which is characterized by serum thyroid hormones within normal limits and a suppressed TSH (subclinical hyperthyroidism). With the further increase of thyroid hormone production, hyperthyroidism evolves from subclinical to clinical, in which an increased level of thyroid hormones is associated with a low TSH (21). The molecular mechanisms involved in the development of thyroid functional autonomy have recently been partially identified. TSH receptor or $G_{s\acute{\alpha}}$-protein undergo somatic point mutation that induce a permanent and TSH-independent activation of the adenylate–cyclasepathway (22;23).

Natural history and epidemiology of goitre and iodine nutrition

In many countries, iodine deficiency largely contributes to the high prevalence of diffuse and nodular goitre (24). People with multinodular goitre usually seek medical attention because they occasionally discover a lump in the neck. Sometimes, the increase in the size of the goitre will cause pressure symptoms, such as difficulty in swallowing, cough, respiratory distress, or the feeling of a lump in the throat. Commonly, the goitre is discovered by a physician in the course of an examination for some other condition. Sometimes, the patient seeks medical attention because of cardiac irregularities or congestive heart failure, which proves to be the result of slowly developing thyrotoxicosis.

In studies conducted in areas with adequate iodine intake, a lower prevalence of goitre is usually reported. In the Whickham survey (25), 15.5% of participants had goitres, with a female–male ratio of 4.5:1. In

the Framingham study (26), 1% of participants between 30 and 59 years had multinodular goitres (at thyroid palpation). In an iodine-deficient area, the goitre prevalence was 35% among people aged between 12 and 14 years, and about 70% in people aged between 35 and 75 years (27). The prevalence of thyroid nodules was much higher when evaluated by ultrasound: up to 50% of the general population have thyroid nodules, even when the thyroid is normal at palpation (28). Consequently, autopsy studies have shown the presence of single or multiple nodules in one-half of the population (29).

A few epidemiological studies have evaluated the clinical evolution of goitre. In the Whickham survey (25), 20% of women and 5% of men who had goitres in the initial survey showed no evidence of goitre in a follow-up survey (30). An average growth rate in the multinodular goitre of 5–20% was reported in iodine-sufficient areas (31). On the basis of the results of the Framingham survey, the estimated lifetime risk for developing a nodule is 5–10% (26). Thyroid nodule size can increase, decrease, or remain stable, and thyroid nodules may eventually also disappear over time. Solid nodules more frequently increase, whereas cystic nodules can shrink or disappear. If the goitre has been present for some time, autonomous function of the nodules and eventually hyperthyroidism develop. The rate of progression from euthyroidism to subclinical and overt hyperthyroidism is about 10%. In a Dutch study of 90 people with euthyroid multinodular goitre, mainly women with a mean age of 55 years, eight became hyperthyroid within 7 years, and all of them had autonomous function before becoming hyperthyroid (32). In a study conducted at the Mayo Clinic, 60% of people with multi-nodular goitre over 60 years had thyrotoxicosis (33). The average duration of the goitre before the onset of thyrotoxicosis was 17 years; the longer the goitre had been present, the greater the tendency for thyrotoxicosis to develop. Iodine intake has been shown to modulate the pattern of thyroid diseases in cross-sectional studies comparing populations living in areas characterized by different iodine intake (24). In iodine-deficient countries, non-autoimmune hyperthyroidism is more frequent, being the natural evolution of goitre, the development of thyroid autonomy, and eventually of thyrotoxicosis. On the other hand, studies in populations living in areas with varying iodine intakes, in the UK (30), Denmark, and Iceland (34), have shown that the frequency of thyroid autoimmunity and of hypothyroidism is higher in iodine replete than in iodine deficient populations.

In Denmark, the Danish investigation on iodine intake and thyroid disease (DanThyr) programme has been developed, with the aim of monitoring iodine intake and thyroid diseases that could secure optimal iodine nutrition of the Danish population (35).The first cohort study of DanThyr programme was started before iodine fortification, and took place in and around the city of Aalborg in Jutland, and in Copenhagen (36). The two geographical regions cover the main difference in levels of iodine intake in Denmark caused by different levels of iodine in ground water (36;37), and goitre was more frequent in areas with lower iodine intake. In a survey

conducted in Pescopagano (27), a southern Italian village with mild-to-moderate iodine deficiency, an age-dependent increased prevalence of goitre, thyroid nodularity, and functional autonomy was observed. Overt hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goitre.

Iodine prophylaxis

Since iodine was removed from the soil during the era of wide glaciations, the amount of iodine in potable water, vegetable and animal food in many areas of the world is poor. The endemic goitre is more common in mountainous regions, but is also present in plane and coastal regions. It is more commonly seen in extra-urban populations, especially rural populations, who eat local foods that are low in iodine. In fact, economic status rather than geographical location is the main determinant of the quality of the food and of the iodine content. In many countries salt, bread, and milk are fortified with iodine in efforts to eradicate iodine deficiency. Other sources of iodine are compounds used by industry and agriculture, supplements, disinfectants, and medicines. The most effective method to improve iodine nutrition is through salt iodization (7). Iodization of all salt for human and livestock consumption (universal salt iodination or USI) is not, however, commonly achieved. Iodine is added to kitchen salt at a level of 20–40 mcg/kg of salt in the form of potassium iodide (KI) or potassium iodate (KIO3). The fortification with iodine of baker's salt, drinking water, and irrigation water has been used, but this method is less practical. When iodization of water is not feasible, iodine can be added to oil. Iodized oil can be given orally or by intramuscular injection (200–400 mg of iodine per year). Iodine can be also given as KI (30 mg monthly) or KIO3. In areas where a salt-iodization programme covering at least 90% of households has been sustained for at least 2 years, and the median urinary iodine indicates iodine sufficiency, there is no need to supplement pregnant and lactating women. In other areas, women should be provided with an intake of at least 150 mcg/day of iodine for a long period before conception to restore intra-thyroidal stores and to ensure a better maternal thyroid.

Worldwide status of iodine deficiency

Only a few countries (Switzerland, some of the Scandinavian countries, Australia, USA, and Canada) were completely iodine sufficient before 1990. Since then, a major effort has been made has to introduce salt iodization as a safe, cost-effective, and sustainable strategy to ensure sufficient intake of iodine in deficient areas (38-50). Iodized salt programmes are now implemented in many countries worldwide, and two-thirds of the world's population (71%) is estimated to be covered by iodized salt (1).

The worldwide state of iodine nutrition was reviewed in 2008. The data were based on urinary iodine surveys carried out between 1997 and 2006 in 41 countries, and estimates obtained in 2003 in 89 countries (7). The data covered 92.4% of the world population aged between 6 and 12 years, and showed that 31.5% (264 million) of school-age children had insufficient iodine intakes (below 100 mg/L). The lowest prevalence of iodine deficiency was in the Americas (10.6%), where over 90% of households consumed iodine-enriched salt. The worldwide state of iodine nutrition was again assessed in 2011 (51). In this survey, data on urinary iodine cover 96.1% of the world's population of school-age children. Since 2007, new national data were available for 58 countries. Between 2003 and 2011, the number of iodine-deficient countries decreased from 54 to 32, and the number of countries with adequate iodine intake increased from 67 to 105. A steady progress was observed in Europe, the Eastern Mediterranean, the South-East of Asia and the Western Pacific regions, largely due to strengthened salt iodization programmes and improved monitoring (52); however, only a negligible progress was observed in Africa. Paradoxically, rich European countries lacking specific iodine prophylaxis programmes remain mildly iodine deficient (51). The prevalence of iodine deficiency in Europe has reduced by 30% between 2003 and 2010, but 44% of school-age children still have insufficient iodine intake. Although the UK was considered iodine sufficient for some time, median urinary iodine was 80 mg/L in 14- and 15-year-old school (53). In Italy, iodine deficiency was initially shown in the mountainous regions of the Alps, but subsequent epidemiological studies demonstrated its presence in all areas, particularly in southern and insular regions. Recently, the status of iodine nutrition was assessed in southern Italian regions (54). Urinary iodine was randomly measured in 26,913 participants, and was lower than 100 mcg/L in 64.3% and lower than 50 mg/L in 34.9% of samples. Median urinary iodine in non-urban areas was significantly lower than in urban areas (69 *v* 79 mg/L; $P < 0.0001$).

Iodine prophylaxis and epidemiology of goitre

Iodine supplementation affects the epidemiology and eventually the natural history of goitre. Early Chinese medical writings in around 3600 B.C. were the first to record the decreases in goitre size upon ingestion of seaweed and overcooked sea sponge (55). Although iodine was yet to be discovered, these remedies remained effective, and their use continued globally, as was documented in writings by Hippocrates, Galen, Roger, and Arnold of Villanova in later centuries (55). The discovery of iodine was made incidentally during the early part of the 19th century (55). Shortly after, J.F. Coindet, a physician in Switzerland, published his observations that administration of iodine (as grains in distilled alcohol) was able to decrease the size of his patients' goitres (16).

In 1852, Adolphe Chatin, a French chemist, was the first to publish the hypothesis of population iodine deficiency associated with endemic goitre (56). This was confirmed by Eugen Baumann, who, in 1896, reported the discovery of iodine within the thyroid gland (57). In the 1830s, the French nutritional chemist, Jean Baptiste Boussingault, observed that the prevalence of goitre was increased in areas where naturally occurring iodized salt was infrequently consumed, and recommended the distribution of naturally iodized salt for public consumption. Iodine supplementation, however, primarily through the fortification of table salt, did not begin until the early 1920s, and occurred initially in Switzerland and the USA.

Between 1916 and 1920, the first large-scale trials with iodine were carried out in Akron by Marine and Kimball (58). In that investigation, about 5000 girls between the ages of 11 and 18 years took part. Marine et al. (59) published a series of papers reporting a significantly decreased frequency of goitre in children treated with iodine (0.2%), compared with children who did not receive iodine supplementation (> 25%).

In Switzerland's an iodized salt programme has been operating uninterrupted since 1922. Before its introduction, Switzerland was severely iodine deficient. In 1919, Klinger, noting the success of the US studies, recommended prophylaxis with iodine tablets at Swiss schools and iodized salt for the general population. The first canton in which iodized salt was introduced was Appenzell AR, in 1922, thanks to the efforts of the surgeon Eggenberger (57). He pushed the local government to allow the sale of salt, iodized at 7.5 mg/kg, with spectacular results: goitre in newborns disappeared, no new cretins were born, and goitres in children were reduced in size or disappeared (57).

In the USA, iodized salt first became available on grocery shelves in Michigan in 1924, encouraged largely by the series of reports by Cowie, Marine, and others in the preceding years (59). Before starting the iodine prophylaxis programme, surveys on goitre in schoolchildren and on the iodine content of drinking water were conducted for the first time in four representative counties of this State. The prevalence of goitre was 38.6% among the 65,537 schoolchildren studied. Salt containing potassium iodide (1 part in 5000) was introduced, and by 1929 was reduced to 9% (59). Bursh and Altland in 1952 conducted follow-up surveys of 53,785 participants in the same counties, and found a goitre prevalence of only 1.4%.

In a recent survey conducted in Pescopagano (60), an Italian village with a previous moderate iodine deficiency, the introduction of an iodine prophylaxis programme on a voluntary basis resulted in a significant reduction of the prevalence of goitre (Fig. 1), mainly due to the reduction of diffuse goitres in 2010 compared with the previous survey in 1995 (10.3% *v* 34.0%). The overall prevalence of nodular goitre was not significantly different in the two surveys. When age was taken into account, however, its frequency was significantly lower in 2010 than in 1995 in people aged between 26 and 35 years (3.8% *v* 11.3%); however, no

difference was observed in people aged over 35 years. The absence of a significant difference in the frequency of nodular goitre in people older than 35 years may be because, in most people this age, the process of morphological changes and goitre development started before the increase in iodine intake (60).

Monitoring iodine prophylaxis

The methods for assessing iodine nutrition in populations are as follows: determination of goitre prevalence, urinary iodine concentration, serum TSH level in newborns, and serum thyroglobulin level (Tg) (61). Goitre size can be measured by neck inspection and palpation or by thyroid ultrasonography. Thyroid ultrasound is more sensitive and specific than palpation, but requires valid reference intervals for thyroid volume (62;63). Goitre surveys as indicators of iodine sufficiency are usually carried out in school-age children because participants are easy to recruit, and reflect the actual effect of iodine deficiency in humans. The WHO established a total goitre rate in school children to define the severity of iodine deficiency. Rates below 5.0% indicate iodine sufficiency; 5.0–19.9%, mild deficiency 20.0–29.9%, moderate deficiency, and above 30.0%, severe deficiency (7).

Because more than 90% of dietary iodine is excreted in the urine, measurement of urinary iodine concentration is a reliable index of recent dietary iodine intake (64). Its determination in a population is directly correlated with the frequency of goitre and the disorders of iodine deficiency. A UIC level of less than 100 mg/L in school-aged children indicates insufficient iodine intake; iodine deficiency is severe at less than 20 mg/L, moderate at 20–49 mg/L, and mild at UIC 50–99 mg/L. An adequate UIC value is 100–199 mg/L, and a value greater than 200 mg/L can induce thyrotoxicosis and other adverse effects in susceptible groups (65).

Thyroid-stimulating hormone concentrations obtained during screening to detect congenital hypothyroidism in newborns is useful to assess iodine nutrition, because an increase of TSH is a mechanism though which the fetus adapts to iodine deficiency. Indeed, iodine deficiency causes a shift toward higher TSH values in the neonatal screening of congenital hypothyroidism. A TSH value greater than 5 mU/L in whole blood collected 3–4 days after birth and lasting for a few weeks in more than 3% of newborns indicates iodine deficiency in a population.

Thyroglobulin (Tg) is the most abundant intrathyroidal protein. Serum Tg is higher in iodine-deficient than in iodine-sufficient areas as a consequence of TSH stimulation. The higher rate of goitre and falls quickly with iodine prophylaxis (66).

In the 1990s, iodized salt programmes were introduced in many countries. It was increasingly reported that, in areas previously endemic for goitre, thyroid size decreased as iodine intake increased; however, thyroid

size did not return to normal for months or years after correction of iodine deficiency. Prevalence of goitre also remained elevated (> 5%), particularly among older children and adults (67). This problem was had already been recognized in the early 1800s by Coindet in Geneva, who noted that goitres often did not completely disappear even after long-term treatment with oral iodine (61). Because of this long time lag in the resolution of goitre, the frequency of goitre is difficult to interpret for several years after iodized salt introduction, because it reflects both a population's history of iodine nutrition as well as its present status. A study conducted among school children in an area of Eastern Tuscany (68) showed that the iodized salt prophylaxis was able to prevent the development of goitre in children born after the implementation of iodized salt consumption and further controlled thyroid enlargement in older children; however, it was found to be less effective in reducing goitre size in children exposed to iodine deficiency in the first years of life.

Following recommendations from WHO in 1993 (61), most national monitoring programmes were measuring both the prevalence of goitre and the urinary iodine concentration. In contrast, to the slow response of the goitre frequency, however, urinary iodine concentration rapidly increased into the normal range after the introduction of adequately iodized salt because they reflected recent iodine intake. This resulted in many programmes reporting a discrepancy between the degrees of residual iodine deficiency in the population, as indicated by the urinary iodine concentration compared with the prevalence of goitre (69). This implies that the time lag to normalization of thyroid size after the introduction of iodized salt in an area of chronic iodine deficiency could be a decade or more. To emphasize the limitation of the measurement of the frequency of goitre in judging the short-term efficacy of salt iodization program, in 2000, WHO recommended that the median urinary iodine concentration be used as the primary indicator of the effect of iodized salt. Assessment of goitre by palpation and hopefully by ultrasonography, however, is still a useful tool in areas in which iodized salt has not yet been introduced or when there are concerns that iodine deficiency may be re-emerging (53;70).

Iodine prophylaxis and the spectrum of thyroid diseases

After the introduction of iodine prophylaxis, increased incidences of hyperthyroidism were observed as a result of the development of iodine-induced thyrotoxicosis in people with pre-existing autonomous multinodular goitre (71). In the USA, after the beginning of iodine supplementation in 1924, Hartsock in 1926 described an outbreak of thyrotoxicosis in adults who took iodized salt living in the Great Lakes region (72). This condition is transient and correlated to the level of iodine deficiency and the amount of iodine administered. In 1980 in Switzerland, the iodine content in salt was increased from 7.5 to 15 mg/kg, doubling iodine intake; incidence of toxic nodular

goitre increased by 12% in the first 2 years after the increase, but then declined to a level of only 25% of the initial incidence (73;74).

In Denmark, starting from June 1998, a programme of voluntary use of iodized salt was launched by the Danish Food and Veterinary Administration in cooperation with salt manufactures and the food industry. After 2 years, it turned out that the programme had failed and, therefore, a mandatory programme was introduced during the period July 2000–April 2001(75). The DanTyr program has documented the pattern of thyroid disease after careful introduction of iodized salt (76). The overall incidence rate of hyperthyroidism increased (baseline, 102.8/100,000/ year; after salt iodization 138.7/100,000/year). Hyperthyroidism increased in both sexes and in all age groups, many of the new cases were observed in young people, and were presumably autoimmune in origin. The investigators suggested that further monitoring is expected to show a decrease in the number of elderly people suffering from nodular hyperthyroidism.These data emphasize the importance of regular monitoring of iodine status to detect low and excessive intakes of iodine. In the survey conducted in Pescopagano (60), after the introduction of a iodine prophylaxis programme on a voluntary basis, thyroid autonomy was not observed in younger people (Fig. 2), and was associated with a significant reduction of the frequency of hyperthyroidism caused by toxic nodular goitre in older age. The investigators did not observe an increased frequency of hyperthyroidism after the beginning of iodine prophylaxis as reported in other studies (77;78), conceivably because of the lower level of iodine supplementation in this population. Taken together, these data indicate that iodine prophylaxis is associated with a reduced frequency of thyroid autonomy in younger people, and of toxic nodular goitre in older people. This phenomenon may have a relevant effect on the health of this population, as thyrotoxicosis is associated with increased morbidity, cardiovascular morbidity in particular, which leads to increased mortality, especially in elderly people (79-81).

A potential side-effect of iodine supplementation is the worsening or the induction of autoimmune thyroiditis (82;83). Cross-sectional studies of populations with different iodine intakes in the UK (30), in Denmark, and in Iceland (34) have shown that the frequency of thyroid autoantibodies and hypothyroidism is higher in iodine replete than in iodine deficient populations. Boukis et al. (84) showed that, in people with goitre from a mildly iodine-deficient area in Greece treated with iodized oil, thyroid autoantibodies, undetectable before treatment, became positive in 42.8% of the people 3 and 6 months later. Recently, Pedersen (85) found an increased prevalence of thyroid autoantibodies after the beginning of a cautious iodization programme, supporting the view that even a small increase of iodine supplementation may be associated with an increased thyroid autoimmunity. An increased frequency of hypothyroidism has also been reported after the careful introduction of iodized salt in Denmark (24;85).The DanTyr program (86) has documented a modest increase

of the incidence rate of hypothyroidism in the 7 years after the introduction of the national program of salt iodization (baseline, 38.3/100,000/year; after salt iodization, 47.2/100,000/ year, *v* baseline, relative risk, 1.23; 95% CI, 1.07 to 1.42). A geographic difference was observed because hypothyroidism increased only in the area with previous moderate iodine deficiency. The increase occurred in young and middle-aged adults (87). Similar findings were reported in the Pescopagano survey, in which an increased frequency of thyroid autoantibodies, and of Hashimoto's thyroiditis were observed after the beginning of iodine prophylaxis (88). That study showed that iodine intake modulates the pattern of thyroid diseases, even with slight differences, and below the dose of 150 mcg daily recommended for preventing IDD. Therefore, any level of change in iodine intake modifies the expression of thyroid diseases. Thyroglobulin (Tg) is an important target in iodine-induced autoimmune response, iodine being an essential component of Tg. As far as the induction of thyroid autoimmunity is concerned, the effect of iodine supplementation is correlated with the intrinsic characteristics of Tg, namely its modifications induced by post-translational iodination.

Summary

Iodine is essential for the synthesis of thyroid hormones, and iodine deficiency has several consequences for human health, referred to as iodine deficiency disorders. These range from defective development of the central nervous system during the fetal-neonatal life, to goitre in the adult. Iodine prophylaxis through iodized salt has been shown to exert a pivotal role in abating iodine deficiency disorders. Iodine intake strongly affects the pattern of thyroid diseases reducing the prevalence of goitre, thyroid autonomy and non-autoimmune hyperthyroidism, but increasing the frequency of thyroid autoimmunity and mild hypothyroidism. It is important to underline, however, that iodine-induced adverse effects can be almost entirely avoided by adequate and sustained quality control and monitoring of iodine supplementation. Available evidence clearly confirms that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation (89;90).

Practice Points

- Iodine is essential for the synthesis of thyroid hormones
- Iodine deficiency has multiple adverse effects, including goitre, which is the most common clinical manifestation, and cerebral impairment, ranging from mild cognitive defects to cretinism.
- Iodine prophylaxis, through iodized salt, has been shown to exert a pivotal role in abating the frequency of iodine deficiency disorders.
- Iodine intake strongly affects the pattern of thyroid diseases by reducing the prevalence of goitre, thyroid autonomy, and non-autoimmune hyperthyroidism, but also increases the frequency of thyroid autoimmunity and mild hypothyroidism.
- Available evidence favours the interpretation that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation.

Research agenda

- Both low and excessive intakes of iodine affect the frequency of thyroid disorders. Large prospective epidemiological studies would better define the optimal iodine intake. These data emphasize the importance of regular monitoring of iodine status after the introduction of iodine prophylaxis.
- Thyroglobulin (Tg) is an important target in the iodine-induced autoimmune response, iodine being an essential component of Tg. The effect of iodine is correlated with the intrinsiccharacteristics of Tg, namely its modifications induced by post-translational iodination. The understanding of these changes may shed light on iodine-induced thyroid autoimmunity.

Conflict of interest

The authors have no conflict of interest to disclose

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Legend of figures

Figure 1. Frequency of goiter in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (grey columns). The prevalence of goiter progressively increased with age both in 1995 and 2010 and in each class of age was significantly lower in 2010 compared to 1995, with the exception of subjects older than 75 years. * = $p < 0.001$

Figure 2. Frequency of functional thyroid autonomy in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (grey columns). The frequency of functional thyroid autonomy was not significantly different between 2010 and 1995 in each class of age due to the small number of subjects, but was significantly lower in 2010 than in 1995 in subjects younger than 45 years grouped together (Fischer test $p = 0.004$), while no significant difference was observed in subjects older than 45 years (not shown in figure).

Legend of figures

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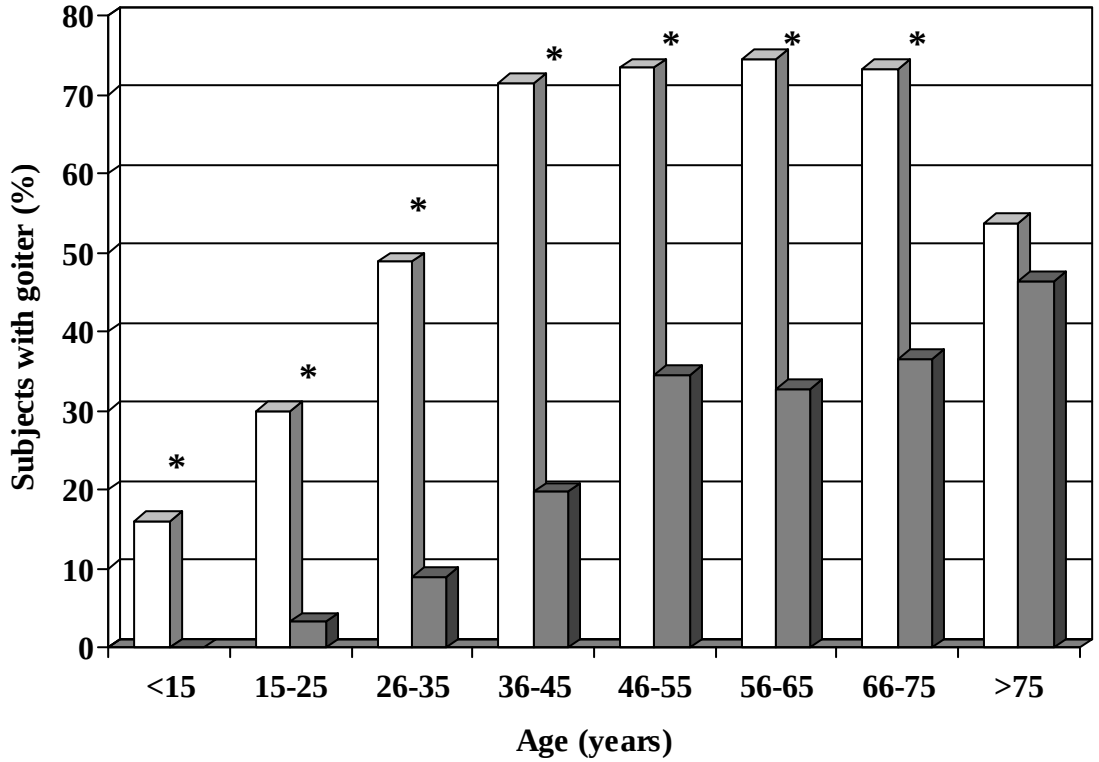

Figure 1

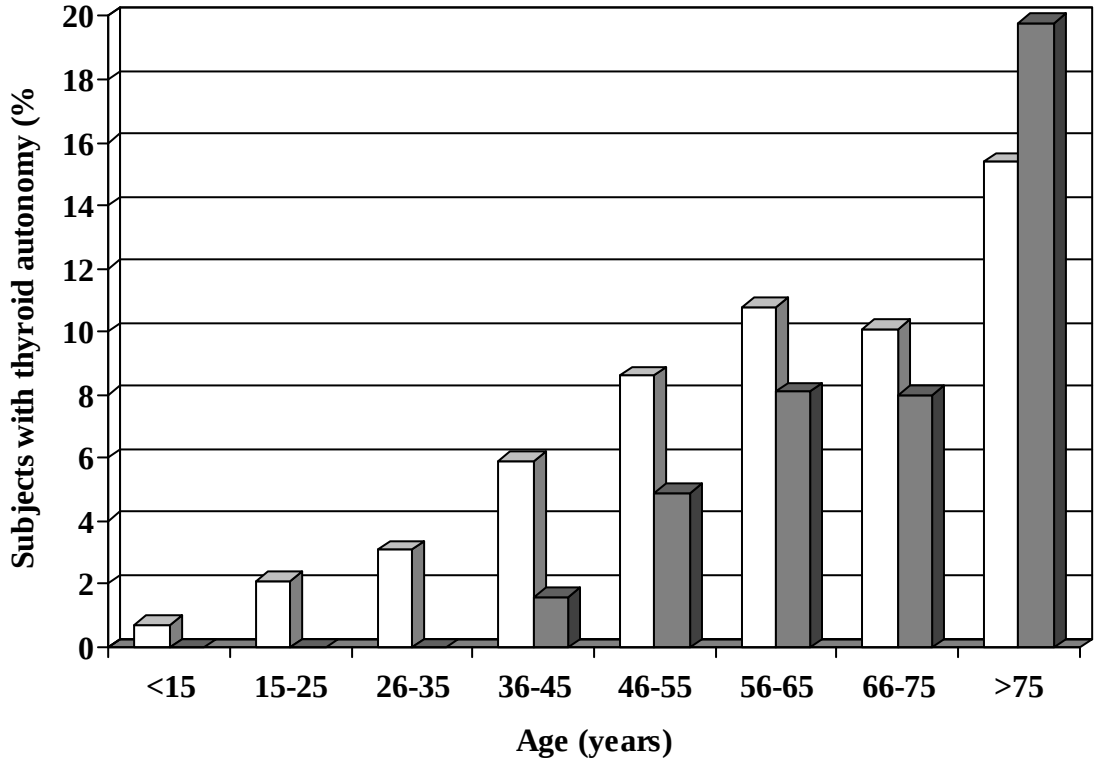

Figure 2