

# Iodine supplementation: Benefits vs Concerns

**Gopalakrishnan Sripathy, Marwaha Raman Kumar**

*Department of Endocrinology & Thyroid Research Centre, Institute of Nuclear Medicine and Allied Sciences, Delhi, India*

### ABSTRACT

IDD encompasses a broad spectrum which includes neurologic cretinism, physical/mental retardation in childhood, goitre and reduced cognitive function and work output. Observational studies on populations and experimental studies have suggested iodine deficiency to be the underlying basis for endemic goitre as well as endemic cretinism. The diagnosis of IDD is made at the level of community and cannot be made at level of individual. Though presence of goitre and cretinism are indicative of iodine deficiency in the community, objective methods are necessary to assess prevalence and severity of iodine deficiency due to the fact that IDD often exists with subtler manifestations. Agencies such as the World Health Organization (WHO), the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the UNICEF jointly proposed various indicators to estimate prevalence of IDD and assess the impact of iodine prophylaxis. Goitre survey remains the most important tool to measure iodine deficiency and estimate the population at risk. In 1999 that nearly 38% of world population spread across 130 countries were affected by IDD making IDD the most common endocrine disorders world wide. The recommended daily dietary intake of iodine varies from 50mg in infant, to 150mg in adult and 200mg during pregnancy and lactation. Provision of iodine in diet is achieved by either universal salt iodisation (USI) or iodized oil as injectable/oral formulations. Despite all the above adverse effects of iodisation reported so far, these have not been found to have major consequences to public health. The safety of iodated salt as the public health approach to eliminate IDD is well known. Benefits of correcting iodine deficiency far outweigh its risks. Iodine induced thyrotoxicosis and other adverse effects can almost be entirely avoided by adequate iodine supplementation and sustained quality assurance and monitoring of programs. [IJEM 2007;(3&4):15-21]

Key words: Iodine deficiency disorders, Iodine, ICCID, endemic goiter, iodine supplementation

### INTRODUCTION

Synthesis of thyroid hormones in sufficient quantities to meet the physiologic demands requires supply of adequate amounts of exogenous iodine(1). It is estimated that a minimum daily intake of 100µg iodine is essential to eliminate all signs of iodine deficiency, though the daily requirement varies between different age groups(2). While iodine is required at all ages, the most critical stages of iodine requirement are during fetal stage and early childhood due to rapid neurological development which takes place at that time. Deficiency of iodine will result in reduced formation of thyroid hormones affecting growth, development and metabolism of various tissues.

The spectrum of manifestations arising from iodine

deficiency in a community is termed 'Iodine Deficiency Disorders' (IDD)(3). IDD encompasses a broad spectrum which includes neurologic cretinism, physical/mental retardation in childhood, goitre and reduced cognitive function and work output. This term was coined to replace 'endemic goitre' which is the most visible manifestation but underestimates the other subtle consequences in the iodine deficient communities.

#### Epidemiology of IDD

Since diet is the sole source of iodine, its intake in human and animal population is dependent on the iodine content of water and soil(1). Land masses which were earlier replete with iodine have been depleted of iodine due to glaciations, rains, floods and repeated cultivation. As a result, vast areas of earth's land mass especially the mountainous regions, rainy areas and previously glaciated regions of the earth are depleted of iodine. In addition to the mountainous regions, its deficiency has also been noted in lowlands and plains of Asia, Africa and Europe(4-7). Observational studies

#### Address for correspondence

Dr RK Marwaha, Division of Thyroid Research, INMAS, Brig. SK Mazumdar Marg, Timarpur, Delhi-110054, India.

Tel: 011- 2393 9684, 011- 2393 4356, Fax: 011- 2391 9509

E-mail: marwaha\_raman@hotmail.com

on populations and experimental studies have suggested iodine deficiency to be the underlying basis for endemic goitre as well as endemic cretinism. This is further supported by the amelioration in IDD seen after iodine prophylaxis. Thus, IDD constitute the most preventable cause of mental retardation and remains a major public health problem around the world.

### IDD Assessment

The diagnosis of IDD is made at the level of community and cannot be made at level of individual. Though presence of goitre and cretinism are indicative of iodine deficiency in the community, objective methods are necessary to assess prevalence and severity of iodine deficiency due to the fact that IDD often exists with subtler manifestations. Agencies such as the World Health Organization (WHO), the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the UNICEF (United Nations International Children's Emergency Fund) jointly proposed various indicators to estimate prevalence of IDD and assess the impact of iodine prophylaxis(8). Goitre survey remains the most important tool to measure iodine deficiency and estimate the population at risk. Other methods used in measuring IDD are: urinary iodine excretion (UIE), thyroid size by ultrasonography (USG), thyroid function tests and prevalence of cretinism.

### Global Prevalence and burden of IDD

It was estimated in 1999 that nearly 38% of world population spread across 130 countries were affected by IDD(6) making IDD the most common endocrine disorders world wide. Out of an estimated world population of 5.8 billion in different regions, 3.8% are estimated to be suffering from iodine deficiency in some form, though only 12% is affected by goitre. In 1994, 43 million were thought to be suffering from some degree of mental handicap as a result of IDD(8). It is known that severe deficiency of iodine exists in most of developing countries and mild to moderate ID exists in parts of Europe though accurate data on global prevalence is lacking.

### Iodine prophylaxis and supplementation

The recommended daily dietary intake of iodine varies from 50ug in infant, to 150mg in adult and 200mg during pregnancy and lactation(2). Provision of iodine in diet is achieved by either universal salt iodisation (USI) or iodized oil as injectable/oral formulations(9). While USI achieves gradual elimination of IDD in whole population, iodized oil delivery through primary health care systems can have rapid impact in select target populations like children/pregnant woman.

### Evolution of iodisation programs

Switzerland and the United States of America (USA) were among the first countries to launch iodisation programs in 1920s. This was done subsequent to recognizing the high prevalence of goitre and cretinism by surveys and the benefit of iodisation by experimental studies(9). Salt iodisation along

with introduction of iodate and iodophores in food industry helped achieve sufficient iodine nutrition in most North American and North European countries(10). Experimental studies were carried out in several countries such as Papua New Guinea, India and others. The positive outcomes from these subsequently triggered launch of widespread campaigns for iodine supplementation around the world(11).

The goal to eliminate IDD from around the globe by the year 2000 was adopted by the World Summit for Children in 1990(6). In its latest recommendation by WHO/UNICEF/ICCIDD, salt iodisation at production site is targeted in the range of 20-40 mg iodine/kg of salt so as to provide the daily requirements of iodine in the adult of about 150µg/d(12). Global campaigns for salt iodisation has achieved remarkable success so much, that by 1995, of 94 countries that had UNICEF programs, 58 had achieved the goal of iodization of 90% edible salt(13). The present article aims to review the benefits achieved vis-à-vis some unwanted effects observed during iodine supplementation programs.

### Iodine supplementation - benefits

#### *World scenario: Goitre prevalence and UIE*

Subsequent to the first experiments with introduction of iodine in diet of local populations in Switzerland, studies showed regression of goitre, reduction in goitre prevalence, increase in average height of children, reduction in incidence of deaf-mutism and prevention of cretinism(14). Similar iodisation program undertaken in USA resulted in total elimination of endemic goitre(15). A recent study conducted 4 years after iodised salt prophylaxis in Cote d'Ivoire, Switzerland found reduction in mean thyroid size (56%), goitre rate (52 to 19%) and normalization of median UIE in children(16).

#### *World scenario: Pregnancy outcomes and offspring*

Several studies were conducted on pregnant women and their offspring in various countries after the women were supplemented with iodine in the form of iodized oil injections. Neonatal outcomes improved and prevalence of goitre and cretinism decreased in Papua New Guinea(17,18). Long term studies in the progeny also showed improvement in the cognitive and motor functions: tests like grip strength, speed of movement, unimanual or bimanual accuracy were performed better by the children in the supplemented group than from control women. There was a salutary effect of iodine supplementation in children born to mothers in terms of school attainments and neuropsychological testing in Ecuador(19,20).

In Zaire, pregnancy outcomes such as birth weight, incidence of infantile chemical hypothyroidism, reduction in perinatal mortality and development quotients of offspring were better in iodine supplemented group as compared to controls(21). The beneficial effects noted in these studies were instrumental in persuading most of countries in Europe, Latin America and South East Asia to work towards IDD elimination by iodine supplementation(9).

*Indian scenario*

The early reports pointed to the presence of endemic goitre and cretinism in the Himalayan belt and Gangetic plains of Uttar Pradesh(22,23,24). The first evidence to show that iodised salt as an effective approach to iodine supplementation came from the results of an experimental study in the Kangra valley between 1956 and 1972(25,26). This group found that goitre prevalence reduced from 35% to 15% in 6 years and to 9% after 12 years of use of iodised salt in the community. This gave the impetus for launching of national goitre control program in 1962, with iodised salt as the major route to provide iodine.

A nationwide study undertaken by the Indian Council of Medical Research (ICMR) found IDD to be endemic in 235 out of 275 districts surveyed and it was estimated that nearly 100 million of the Indian population is at risk of IDD(27). Considering the widespread presence of IDD and the gravity of the problem, National Goitre Control Program (1962) was re-designated as National Iodine Deficiency Disorders Control Program (NIDDCP) in 1992 with adoption of universal salt iodisation as its main strategy for control and sustained elimination of IDD.

While USI gained wide acceptance with the medical community, iodized oil injections did not find favour except for an experimental study which used iodized oil in two districts of UP(28). Regardless of the approach used for iodine supplementation, studies showed benefits in terms of improvement in UIE and reduction in goitre prevalence.

Most of studies that have evaluated the impact of universal salt iodisation have relied on goitre prevalence and urinary iodine excretion (UIE) as indicators. Studies from Delhi as well as other regions of the country revealed adequate median UIE in school children(29,30,31). Goitre prevalence (GP) has also been shown to be declining in the country, as for example in Delhi, the GP reduced from 55% in 1983 to 19% and 9.2% in later studies(30, 31).

Following the USI campaign, there has been significant improvement in iodine nutrition in terms of UIE and iodine content of salt(31,32). There is also indirect evidence of better iodine nutrition in terms of reduction in size of the gland in terms of goitre grade with more than 90% goiters seen in surveys to be of grade 1(29,30). The prevalence of thyroid nodules is also low (0.04%), though pre-iodisation data is not available in this regard. Similarly, two recent studies, one in pregnant women and another in children showed iodine sufficiency(33,34).

The effect of iodine deficiency on neurodevelopment was shown by Kochupillai *et al* when they found that 56% of schoolchildren in iodine deficient villages of this country had intelligence quotient (IQ) less than 80 compared to 9% in non-endemic areas(35,36). It was also seen that more than 80% of children in endemic villages had IQ less than 90. Follow up studies after iodisation program clearly revealed drastic improvement in IQ as shown in table 1 (personal communication- Prof Manju Mehta).

**Table 1:** Comparison of intelligence quotient (MISIC) in school going children from District Gonda, Uttar Pradesh, India

	IQ distribution expressed as percentage					
	< 69	70-79	80-89	90-109	110-119	>120
Year 2001 (n = 60)	-	8.3	16.7	51.7	18.3	5
Year 1986 (n = 60)	23.3	33.3	25	16.7	1.7	0

(Courtesy: Prof. Manju Mehta, AIIMS, New Delhi)

All these studies are indicative of widespread benefits as well as remarkable success in the nationwide iodisation being pursued under the National Iodine Deficiency Disorders control programme by the Government of India.

### Iodine supplementation – concerns

Though supplementation of iodine is associated with large scale benefits, concerns have been raised regarding side effects due to the complex nature in which different levels of iodine act on thyroid gland. Though evidence from studies show that iodine intake up to 1mg/day could be tolerated by normal adults(37,38), this was not reassuring enough due to accumulation of evidence to the contrary. Continued exposure to iodine at levels higher than required daily intake may result in clinical conditions like goitre, hypothyroidism, autoimmunity and others. (It is thought that these are more likely to occur during iodine supplementation in iodine deficient populations).

### Thyrotoxicosis

Iodine induced thyrotoxicosis (IIT) was first reported from Tasmania and has since been observed in most of iodisation programs(39,40). The outbreak occurred in Tasmania following iodine supplementation by iodine tablets, iodized bread and use of iodophores in the milk industry. The incidence increased from 24/100,000 in 1963 to 125/100,000 in 1967 and occurred more frequently in people over 40 years of age and those with multi-nodular goiters. Epidemic lasted for 10-12 years, after which incidence of thyrotoxicosis fell below that prior to the epidemic despite continued iodisation.

A sharp increase in incidence of thyrotoxicosis from 3/100,000 to 7/100,000 was observed in Zimbabwe over 18 months of introduction of iodised salt(41). High risk of iodine induced hyperthyroidism was also reported from Kivu, Zaire following iodised salt introduction(42). A multi-centric study in 7 African countries including Congo and Zimbabwe showed that thyrotoxicosis stemmed from sudden induction of excessively iodised salt in severely iodine deficient population for a long time(43). In Switzerland, an increase in incidence of thyrotoxicosis by 27% was seen during the year after level of iodine supplementation was increased from 90µg/day to 150µg/day(44). Similarly, introduction of iodised salt in China with borderline deficiency resulted in slight but significant increase in the incidence of thyrotoxicosis(45).

In variance to the above reports, two controlled studies using iodized oil in iodine deficient population of Iran, and Romania did not find any increase in incidence of IIT while goitre prevalence decreased(46, 47, 48). A recent study from three provinces of China with mild iodine deficiency (UIE 84  $\mu\text{g}/\text{lit}$ , Panshan), more than adequate iodine intake (243  $\mu\text{g}/\text{lit}$ , Zhangwa) and excessive iodine intake(651  $\mu\text{g}/\text{lit}$ , Huangwa) respectively showed no association of increase in iodine with hyperthyroidism(49). Other studies did not reveal any excess occurrence of hyperthyroidism after iodine prophylaxis (50,51). Study on thyroid function during goiter surveys in India also did not show hyperthyroidism though the country is undergoing iodisation for last two decades(30, 51).

It appears that while benefits of iodisation are overwhelming, it could result in IIT especially in the early phase, in individuals with pre existing nodular disease, in the absence of adequate monitoring of the programs.

### Goitre and autoimmunity

It has been suggested that iodine supplementation could induce/aggravate autoimmunity resulting in goitre and thyroid dysfunction as evident from animal studies, experimental studies on humans and population studies. The first observations were made in chicken and rats when experimental autoimmune thyroiditis (EAT) was induced on administration of iodine(52, 53). This hypothesis was further supported by population studies from USA and Japan which showed higher prevalence of AIT in parallel with higher iodine intake(54,55,56). Iodinated contrast agents and amiodarone which contain large amounts of iodine are also reported to induce AIT in certain individuals(57).

Lymphocytic infiltration of thyroid gland and development of antithyroid antibodies in serum were reported following iodisation programs in countries such as USA, Greece(58,59). Increased production of anti-thyroid antibodies in association with increase in iodine intake was first reported after introduction of iodised oil in Greece and Italy (60,61). In Epirus which was under salt iodisation for 3 decades, overall prevalence of AIT by thyroid antibodies was 3.3% & goitre specific prevalence was 16.5%(62).

A study on schoolchildren from Delhi, India found autoimmune thyroiditis (positive anti-microsomal or anti-thyroglobulin or both) in 112 of 396 goitrous subjects out of 4320 children(30). This study also reported direct correlation between urinary iodine excretion (UIE) and autoimmunity with goitre and autoimmunity with thyroid dysfunction (subclinical hypothyroidism). In China, autoimmune thyroiditis was found to be associated with more than adequate or excess iodine but no such relation of iodine status with thyroid antibodies alone(49).

Though rising incidence of thyroid autoimmunity is reported by above studies, other studies using iodine have failed to find similar evidence(63). Two population studies from India and studies from iodine deficient and replete areas of Europe did not show any correlation between UIE and

thyroid autoimmunity(51, 64, 65, 66). A one year prospective trial in Northern Morocco following introduction of iodised salt showed a transient increase in anti-thyroglobulin antibodies but the antibody levels returned to baseline after 1 year(67). Similar findings were reported from Sri Lanka but pre-iodisation status was unknown(68).

### Iodine nutrition and thyroid dysfunction

Some studies point to increasing thyroid dysfunction with increased iodine intake possibly due to iodine directly suppressing thyroid function as well as iodine inducing autoimmune thyroiditis. A recent study from three different regions of China with differing iodine intake, increased iodine intake was associated with increase in prevalence of overt and subclinical hypothyroidism(49). The cumulative incidence of supranormal thyrotropin (TSH) among euthyroid subjects with positive antithyroid antibodies increased with increasing iodine intake in all the three cohorts(49). In another study on children from Delhi, the median UIE in children with subclinical hypothyroidism ( $17.6 \pm 3.4 \mu\text{g}/\text{dl}$ ) was significantly higher than in euthyroid children with autoimmune thyroiditis ( $14.7 \pm 4.4$ ;  $p < 0.001$ )(30). High prevalence of raised TSH ( $>5 \mu\text{IU}/\text{l}$ ) in 32.4% seen 3 years after introduction of iodised salt in Car Nicobar Islands in Bay of Bengal (69 mallik).

Other studies do not corroborate the above evidence linking iodine with thyroid dysfunction. In United States, National Health and Nutrition Evaluation Survey (NHANES III) did not find any correlation between UIE and thyroxine (T4) or TSH(10). Similarly, one countrywide study from India also did not show any correlation between urinary iodine and thyroid function(29, 51).

### Iodine nutrition and goiter

It is suggested that excessive iodine could cause goitre due to iodine induced increase in autoimmune thyroiditis as well as iodine induced block of thyroid hormone release causing increase in TSH and goitre. Higher median urinary iodine was shown in goitrous subjects compared to controls in a cross sectional study of school children in India(29). In Delhi, India direct correlation of UIE with goitre was seen in presence of autoimmune thyroiditis but not otherwise(30). A large prospective study from China showed goitre correlation with mild iodine deficiency as well as excess iodine intake(49). A large international study showed direct relation of urinary iodine  $>50 \mu\text{g}/\text{dl}$  with thyroid volume but not for 30-50  $\mu\text{g}/\text{dl}$  range(70).

### Iodine and thyroid neoplasia

The existence of a relationship between occurrence of thyroid cancer and iodine status continues to be debated. In experimental studies on iodine deficient animals, increased development of thyroid carcinomas was seen(71,72). It was proposed that chronic stimulation due to raised TSH seen in such animals may induce neoplasia in thyroid, but whether this could play a role in areas of endemic goitre is not clear.

The overall incidence of thyroid carcinoma in a population is not thought to be influenced by iodine

intake(73). In Italy, incidence of thyroid carcinoma was higher in an iodine-deficient area compared to that in an iodine-sufficient region(74). On the other hand, studies from Iceland and Hawaii which are areas of high iodine intake, the incidence was initially linked to iodine intake, but this could also be due to higher natural radiation in these volcanic areas (75,76). Reduction in incidence of thyroid cancer from 2-3/100,000 in 1950 to 1-2/100,000 in 1998 was seen in Switzerland, after iodine supplementation(77). Similarly, after iodine prophylaxis in Poland, fine needle aspiration of 3572 patients over a period of 15 years (1985-1999) found significant decrease in neoplastic lesions and increase in ratio of papillary to follicular carcinoma(78).

There is a distinct change in the type of carcinomas in thyroid gland following iodisation in deficient populations. The ratio of papillary to follicular carcinomas rose in Argentina and Switzerland(79,80). These studies and others denote changes in epidemiological pattern of thyroid cancer subsequent to iodine prophylaxis, with probable improvement in prognosis due to shift towards more differentiated forms of thyroid cancer that are diagnosed at earlier stages(81).

Data on this aspect is scanty from India with one study reporting that course and outcome of differentiated thyroid cancer in children from iodine deficiency areas is no different from those in iodine sufficient areas(82).

## SUMMARY OF EVIDENCE AND CONCLUSIONS

Despite all the above adverse effects of iodisation reported so far, these have not been found to have major consequences to public health. The safety of iodated salt as the public health approach to eliminate IDD is well known. Benefits of correcting iodine deficiency far outweigh its risks. Iodine induced thyrotoxicosis and other adverse effects can almost be entirely avoided by adequate iodine supplementation and sustained quality assurance and monitoring of programs.

## REFERENCES

- Larsen PR, Davies TF, Schlumberger MJ, Hay ID. Thyroid Physiology & diagnostic evaluation of patients with thyroid disorders. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS (eds) Williams Textbook of endocrinology, 10th edition. Philadelphia, Saunders, 2002 p331-373.
- National Research Council. Recommended dietary allowances, 10th ed. Washington DC, National Academy of Sciences, 1989.
- Hetzel BS. The story of iodine deficiency: an international challenge in nutrition. Oxford university press, Delhi. 1989.
- Stanbury JB, Hetzel BS. Endemic goiter and cretinism: iodine nutrition in health and disease. New York, John Wiley and Sons, 1980. p1-606.
- Hetzel BS, Dunn JT, Stanbury JB. The prevention and control of iodine deficiency disorders. Amsterdam, Elsevier Science, 1987. p 1-354.
- WHO/UNICEF/ICCIDD. Progress towards the elimination of iodine deficiency disorders(IDD). Geneva:World Health Organization;1999. Publication WHO/NHD/99.4:1-33.
- Koutras DA, Matovinovic J, CVought R. The ecology of iodine. In: Stanbury JB, Hetzel BS eds. Endemic goiter and endemic cretinism. New York, JohnWiley and Sons, 1980. p185-95.
- WHO/UNICEF/ICCIDD. Indicators for assessing iodine deficiency disorders and their control through salt iodization. Geneva: World Health Organization:1994. Publication WHO/NUT/94.6.
- Hetzel B S. Recent progress in the elimination of Iodine deficiency disorders. In: Hetzel B S, Pandav C S. S.O.S for a billion, The conquest of iodine deficiency disorders. Delhi, Oxford University press, 1996, page 31-56.
- Soldin OP, Tractenberg RE, Pezzullo JC. Do thyroxine and thyroid-stimulating hormone levels reflect urinary iodine concentrations? Ther Drug Monit. 2005;27: 178-85.
- Delange F M, Dunn J T. Iodine deficiency. In: Braverman L E, Utiger R D. (eds) Werner & Ingbar's The Thyroid, A fundamental and clinical text, 9th edition, Philadelphia, Lippincott, Williams & Wilkins 2004, p 204-305.
- WHO/UNICEF/ICCIDD. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. Geneva: World Health Organization; 1996. WHO/NUT/96.13: 1-9.
- UNICEF. The progress of nations. New York: United Nations Children's Fund; 1995:1-54.
- Burgi H, Supersaxo Z, Selz B. Iodine deficiency diseases in Switzerland one hundred years after Theodor Kocher's survey: A historical review with some new goitre prevalence data. Acta Endocrinologica (Copenh) 1990; 123: 577-90.
- Marine D, Kimball OP. The prevention of simple goitre in man. Am J Med Sci 1922: 163-634.
- Zimmermann MB, Hess SY, Adou P, Toresanni T, Wegmiller R, Hurreli R F. Thyroid size and goitre prevalence after introduction of iodized salt: a 5 year prospective study in schoolchildren in Cote d'Ivoire. Am J Clin Nutr 2003 ;77: 663-7.
- Pharoah POD, Buttifield IH, Hetzel BS. The effect of iodine prophylaxis on the incidence of endemic cretinism. In: Stanbury JB, Kros RL eds. Human Development and the thyroid gland; Relation to endemic cretinism. New York, Plenum Press, 1972; 201.
- Pharoah POD, Buttifield IH, Hetzel BS. Neurological damage to the foetus resulting from severe iodine deficiency during pregnancy. Lancet 1971;ii: 308-10.
- Pharoah POD, Connolly KJ. A controlled trial of iodinated oil for the prevention of endemic cretinism. A long term follow up. Int J Epidemiol 1987;16: 68-73.
- Fierro-Benitez R, Cesar R, Stanbury JB, Rodrigouez P, Garces F, Fierro-Reno F, *et al*. Effects on schoolchildren of prophylaxis of mothers with iodized oil in an area of iodine deficiency. J Endocrinol Inv 1988;11: 327-35.
- Thilly CH, Lagasse R, Bourdoux P, Ermans AM. High dose iodine prophylaxis in severe endemic goitre. A balance of risks. J Mol Med 1980;4: 191-7.
- McCarrison R, Newcomb C, Viswanath B, Norris RV. Ind J Med Res 1927;15: 207.
- Stott H, Bhatia BB, Lal RS, Rai KC. Ind J Med Res 1931 ; 18: 1059
- Ramalingaswami V, Subramanian TAV, Deo MG. The aetiology of Himalayan endemic goitre. Lancet 1961;1: 791-4.
- Sooch SS, Ramalingaswami V. Preliminary report of an experiment in the Kangra valley for the prevention of Himalayan endemic goitre with iodized salt. Bull World Health Organ 1965;32: 299-315.
- Sooch SS, Deo MG, Karmarkar MG, Kochupillai N, Ramachandran K, Ramalingaswami V. Prevention of endemic goitre with iodised salt. Bull World Health Organ 1973;49: 307-12.

27. Indian Council of Medical Research. Epidemiological survey of endemic goitre and endemic cretinism. An ICMR task force study. ICMR, New Delhi, 1989.
28. Sankar R, Pandav CS, Ahmed FU, Rao P, Dwivedi MP, Desai V, *et al*. Review of experiences with iodized oil in national programmes for control of Iodine Deficiency Disorders. *Ind J Pediatr* 1995;62: 381-93.
29. Marwaha RK, Tandon N, Gupta N, Karak AK, Verma K, Kochupillai N. Residual goitre in the postiodization phase: iodine status , thiocyanate exposure and autoimmunity. *Clin Endocrinol (Oxf)* 2003;59: 672-81.
30. Gopalakrishnan S, Singh SP, Prasad WR, Jain SK, Ambaradar VK, Sankar R. Prevalence of goitre and autoimmune thyroiditis in schoolchildren in Delhi, India, after two decades of salt iodisation. *J Pediatr Endocrinol Metab* 2006;19: 889-93.
31. Pandav CS, Mallik A, Anand K, Pandav S, Karmarkar MG. Prevalence of iodine deficiency disorders among schoolchildren of Delhi. *Natl Med J Ind* 1997;10: 112-4.
32. Kapil U, Sethi V, Goindi G, Pathak P, Singh P. Elimination of iodine deficiency disorders in Delhi. *Ind J Pediatr* 2004;71: 211-2.
33. Chakraborty I, Chatterjee S, Bhadra D, Mukhopadhyaya BB, Dasgupta A, Purkait B. Iodine deficiency disorders among the pregnant women in a rural hospital of West Bengal. *Ind J Med Res* 2006 ; 123 : 825-9
34. Sivakumar B, Nair KM, Sreeramulu D, Suryanarayana P, Ravinder P, Shatrugna V, *et al*. Effect of micronutrient supplement on health and nutritional status of schoolchildren: biochemical status. *Nutrition*. 2006;22(1Suppl): S15-25.
35. Kochupillai N, Pandav CS, Godbole MM, Ahuja MMS. *Bul WHO* 1986;64: 547-51.
36. Kochupillai N, Pandav CS. In: Hetzel BS, Stanbury JB (eds). *Prevention and control of iodine deficiency disorders*. New York, Elsevier, 1984. p 203-12.
37. Thomson CD. Dietary recommendations of iodine around the world. *IDD Newsletter* 2002;18: 38-42.
38. WHO. Iodine and health, eliminating iodine deficiency disorders safely through salt iodization. World Health Organization, Geneva, 1994, p 1-7,
39. Stanbury JB, Ermans AE, Bordoux P, Todd C, Oken E, Tonglet R, *et al*. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* 1998;8: 83-100.
40. Connolly RJ, Vidor GI, Stewart JC. Increase in thyrotoxicosis in endemic goitre area after iodation of bread. *Lancet* 1970;1(7645): 500-2
41. Todd CH, Allain T, Gomo ZA, Hasler JA, Ndiweni M, Oken E. Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe. *Lancet* 1995;346: 1563-4.
42. Bourdoux P, Ermans AM, Mukalay WA, Mukalay A, Filetti S, Vigneri R. Iodine-induced thyrotoxicosis in Kivu, Zaire. *Lancet* 1996;347: 552-3.
43. Delange F, de Benoist B, Alnwick D. Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999;9: 545-56.
44. Baltisberger BL, Minder CE, Bürgi H. Decrease of incidence of toxic nodular goitre in a region of Switzerland after full correction of mild iodine deficiency. *Eur J Endocrinol* 1995;132: 546-9.
45. Yang F, Teng W, Shan Z, Guan H, Li Y, Jin Y, *et al*. Epidemiological survey on the relationship between different iodine intakes and the prevalence of hyperthyroidism. *Eur J Endocrinol* 2002;146: 613-8.
46. Azizi F, Daftarian N. Side-effects of iodized oil administration in patients with simple goiter. *J Endocrinol Invest* 2001;24: 72-7.
47. Mirmiran P, Kimiagar M, Azizi F. Three-year survey of effects of iodized oil injection in schoolchildren with iodine deficiency disorders. *Exp Clin Endocrinol Diabetes* 2002;110: 393-7.
48. Simescu M, Varcui M, Nicolaescu E, Gnat D, Podoba J, Mihaescu M, *et al*. Iodized oil as a complement to iodized salt in schoolchildren in endemic goiter in Romania. *Horm Res* 2002;58: 78-82.
49. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, *et al*. Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 2006; 354: 2783-93.
50. García-Mayor RV, Ríos M, Fluiters E, Méndez LF, García-Mayor EG, Andrade A. Effect of iodine supplementation on a pediatric population with mild iodine deficiency. *Thyroid* 1999;9: 1089-93.
51. Marwaha RK, Tandon N, Gupta N, Karak AK, Verma K, Kochupillai N. Residual goitre in the postiodization phase: iodine status, thiocyanate exposure and autoimmunity. *Clin Endocrinol (Oxf)*. 2003;59: 672-81.
52. Bagchi N, Brown TR, Urdanivia E, Sundick RS. Induction of AIT in chickens by dietary iodine. *Science* 1985;230: 325-327.
53. Allen EM, Appel MC, Braverman LE. Iodine-induced thyroiditis and hypothyroidism in the hemithyroidectomized BB/W rat. *Endocrinology* 1987;121: 481-5.
54. Laurberg P. Iodine intake - what are we aiming at?. *J Clin Endocrinol Metab* 1994;79: 17-9.
55. Hall R, Lazarus JH. Changing iodine intake and the effect on thyroid disease. *Br Med J* 1987;294: 721-2.
56. Inoue M, Taketani N, Sato T, Nakajima H. High incidence of chronic lymphocytic thyroiditis in apparently healthy schoolchildren: epidemiological and clinical study. *Endocrinol Jpn* 1975;22: 483-8.
57. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev* 2001;22: 240-54.
58. McConahey WM, Keating FR, Beahr OH *et al*. On the increasing occurrence of Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 1962;22: 542-4.
59. Kahaly GJ, Dienes HP, Beyer J, Hommel G. Iodide induces thyroid autoimmunity in patients with endemic goitre: a randomised double-blind, placebo-controlled trial. *Eur J Endocrinol* 1998;139: 290-7.
60. Boukis MA, Koutras DA, Souvatzoglou A, Evangelopoulou A, Vrontakis M, Mouloupoulos SD. Thyroid hormone and immunological studies in endemic goitre. *J Clin Endocrinol Metab* 1983;57: 859-62.
61. Fenzi GF, Giani C, Ceccarelli P, Bartalena L, Macchia E, Aghini-Lombardi F, *et al*. Role of autoimmune and familial factors in goiter prevalence. Studies performed in a moderately endemic area. *J Endocrinol Inv* 1986;9: 161-4.
62. Tsatsoulis A, Johnson EO *et al*. Thyroid autoimmunity is associated with higher urinary iodine concentrations in an iodine-deficient area of Northwestern Greece. *Thyroid* 1999;9: 279-83.
63. Knobel M, Medeiros-Neto G. Iodized oil treatment for endemic goitre does not induce surge of positive serum concentrations of anti-thyroglobulin or anti-microsomal autoantibodies. *J Endocrinol Inv* 1986;9: 321-4.
64. Marwaha RK, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in post-iodization phase in India. *J Clin Endocrinol Metab* 2000;85: 3798-802.
65. Loviselli A, Velluzzi F, Mossa P, Cambosu MA, Secci G, Atzeni F, *et al*. Sardinian School children Study Group. The Sardinian Autoimmunity Study: 3. Studies on circulating antithyroid antibodies in Sardinian schoolchildren: relationship to goiter prevalence and thyroid function. *Thyroid* 2001;11(9): 849-57.
66. Kabelitz, M, Liesenkotter KP, Stach B, Willgerodt H, Stablein W,

- Singendonk W, *et al*. The prevalence of antithyroid peroxidase antibodies and autoimmune thyroiditis in children and adolescents in an iodine replete area. *Eur J Endocrinol* 2003;148(3):301-7.
67. Zimmermann MB, Moretti D, Chaouki N, Torresani T. Introduction of iodized salt to severely iodine-deficient children does not provoke thyroid autoimmunity: a one-year prospective trial in northern Morocco. *Thyroid* 2003;13(2): 199-203.
68. Mazziotti G, Premawardhana LD, Parkes AB, Adams H, Smyth PP, Smith DF, *et al*. Evaluation of thyroid autoimmunity during iodine prophylaxis-the Sri Lankan experience. *Eur J Endocrinol* 2003; 149(2): 103-10.
69. Mallik AK, Pandav CS, Achar DP, Anand K, Lobo J, Karmarkar MG, *et al*. Iodine deficiency disorders in Car Nicobar (Andaman and Nicobar Islands). *Natl Med J India* 1998;11: 9-11.
70. Zimmermann MR, Ito Y, Hess SY, Fujieda K, Molinari L. High thyroid volume in children with excess dietary iodine. *Am J Clin Nutr* 2005;81: 840-4.
71. Schaller RT, Stevenson JK. Development of carcinoma of the thyroid in iodine-deficient mice. *Cancer* 1966;19: 1063-80.
72. Fortner JG, George PA, Sternberg SS. Induced and spontaneous thyroid cancer in the Syrian (golden) hamster. *Endocrinology* 1960; 66: 364-76.
73. Kaplan MM, ed. *Thyroid carcinoma*. *Endocrinol Metab Clin North Am* 1990;19: 469-766.
74. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, *et al*. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age and multinodularity. *Am J Med* 1992;93: 363-9.
75. Williams ED, Doniach I, Bjarnason O, Michie W. Thyroid cancer in an iodide rich area: A histopathological study. *Cancer* 1977 ; 39 : 215-22.
76. Goodman MT, Yashizawa CN, Kolonel LN. Descriptive epidemiology of thyroid cancer in Hawaii. *Cancer* 1988;61: 1272-81.
77. Levi F, Vecchia, CL, Randriamiharisoa A . Cancer mortality in Switzerland 19889 *Soz Preventimed* 1991;36: 112-26.
78. Slowinska-Klencka D, Klencki M, Sporny S, Lewinski AI. Fine-needle aspiration biopsy of the thyroid in an area of endemic goitre : influence of restored sufficient iodine supplementation on the clinical significance of cytologic results. *Eur J Endocrinol* 2002; 146: 19-26.
79. Harach HR, Escalante DA, Onativia A, Lederer Outes J, Saravia Day E, *et al*. Thyroid carcinoma and thyroiditis in an endemic goitre region before and after iodine prophylaxis. *Acta Endocrinol (Copenh)* 1985;108: 55-60.
80. Langsteger W, Koltringer P, Wolf G. The impact of geographical , clinical, dietary and radiation-induced features in epidemiology of thyroid cancer. *Eur J Cancer* 1993;29A: 1547-53.
81. Feldt-Rasmussen U. Iodine and cancer. *Thyroid* 2001;11: 483-6.
82. Bal CS, Padhy AK, Kumar A. Clinical features of differentiated thyroid carcinoma in children and adolescents from a sub-Himalayan iodine-deficient endemic zone. *Nucl Med Commun*. 2001;22: 881-7.