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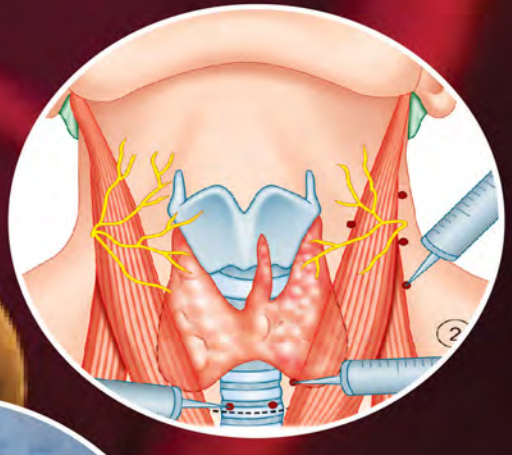



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3rd Edition

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CHAPTER 3

Endemic Iodine Deficiency and Goiters: Epidemiology, Pathophysiology and Management

Gaurav Agarwal, Gitika Nanda

INTRODUCTION

Goiter, an enlargement of the thyroid gland, is considered *endemic* when it affects >10% of the population in a defined geographic area as a consequence of iodine deficiency. Such an area is called an *endemic iodine-deficient region*.[1] As per a decision made by the World Health Organization (WHO)/United Nations International Children's Emergency Fund (UNICEF)/International Council for the Control of Iodine Deficiency Disorders (ICCIDD) consultation on iodine deficiency disorder (IDD) prevalence in November 1992, overall goiter prevalence of 5% or higher in a population should indicate a public health problem of iodine deficiency.[2] The effects of iodine deficiency on human growth and development are collectively referred to as IDDs (Table 3.1).[3] Endemic goiter is the chief consequence of iodine deficiency, resulting from either low iodine intake or ingestion of goitrogens. IDDs and endemic goiters are a global public health problem, affecting a vast majority of the world population. According to 2007 statistics from the WHO, about 2 billion people around the world have insufficient dietary iodine intake.[4]

Iodine deficiency affects all stages of development starting from in utero to neonatal period, infancy, childhood, and adolescence (Table 3.1). Severe iodine deficiency affects the developing central nervous system. During pregnancy, severe iodine deficiency can result in spontaneous abortion or stillbirth, and congenital anomalies or cretinism in the newborn. In children and adolescents, it produces problems ranging from mild intellectual impairment, mental retardation to overt endemic cretinism. It is well recognized that a borderline iodine deficiency too can result in some degree of motor deficit or developmental delays, such as poor hand–eye coordination and impaired intellectual performance exemplified by a reduction in IQ scores by as much as 10–15 points in tests of mental development.[5] In the year 1999, WHO started a global initiative of universal salt iodization (USI) with the aim of elimination of IDD and endemic goiters by the year 2000. Though the goal of elimination of IDD has not been achieved, this program has made spectacular progress over the last 25 years.

Table 3.1: Spectrum of iodine-deficiency disorders

Stage of development	*Disorder*
Fetus	Abortions Stillbirths Congenital anomalies Increased perinatal mortality Increased infant mortality Neurologic cretinism (mental deficiency, deaf-mutism, spastic diplegia, squint) Myxedematous cretinism (dwarfism, mental deficiency) Psychomotor defects
Neonate	Neonatal goiter Neonatal hypothyroidism
Child and adolescent	Goiter Juvenile hypothyroidism Impaired mental function Retarded physical development
Adult	Goiter with its complications Hypothyroidism Impaired mental function Iodine-induced hyperthyroidism
All ages	Increased susceptibility to nuclear radiation

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The clinical presentation of endemic goiter may vary from a diffuse goiter to multinodular goiter (MNG). Long-standing goiters may become autonomous in function and produce hyperthyroidism. Mechanical obstruction to the trachea and the thoracic inlet and malignant progression are other possible sequel of long-standing endemic goiters. Biochemically, patients may have low urinary iodine (UI) excretion levels, and low or normal serum thyroxine (T_4) levels with an elevated serum thyroid-stimulating hormone (TSH) level. Prevention of goiters by appropriate public health interventions, most important being USI is the most desirable management strategy. As endemic goiters are a direct manifestation of iodine deficiency, the study of their prevalence, pathophysiology, and prevention would almost entirely be related to eradicating iodine deficiency itself. However, once formed, endemic goiters are managed with iodine supplementation and levothyroxine (LT_4) suppressive therapy to reverse (subclinical) hypothyroidism and to possibly reduce the size of the goiter. For long-standing goiters, the treatment is the same as that for sporadic goiter: thyroidectomy (Tx) is advocated when appropriate based on presence of compressive symptoms, or suspicion of malignancy; and radioactive iodine (RAI) therapy is used selectively.

This chapter aims to provide an overview of the epidemiology of iodine deficiency and endemic goiters, the various public health programs aimed at preventing them, the effect such programs have had on iodine deficiency and endemic goiter prevalence, and evaluation and medical and surgical treatment of endemic goiters.

EPIDEMIOLOGY OF IODINE DEFICIENCY AND ENDEMIC GOITERS

The daily iodine intakes in most parts of the world are less than the recommended daily intake for various age groups (Table 3.2). As a result, IDD and endemic goiters remain a major public health problem. The global prevalence of endemic goiter is 15·8%, and varies widely between various regions, with the highest prevalence in the Eastern Mediterranean (37·3%) and the lowest in the United States (4·7%) according to 2005 WHO statistics.[6] Epidemiologic studies are usually carried out in school-age children (6–12 years of age) owing to their high physiologic vulnerability and their accessibility through schools for studies on baseline health parameters, as well as effect for studying impact of public health programs and interventions.[7] The interpretation of the WHO data should be done with caution, as it is based on representative regional studies, which cover about 60% of the global population[4], and as such studies can underestimate or overestimate the extent of iodine deficiency worldwide.

Table 3.2: Recommended daily intake of iodine

	Age	*RDA of iodine*
Pre-school children	0 to 59 months	90 micrograms/day
School children	6 to 12 years	120 micrograms/day
Adults	Above 12 years	150 micrograms/day
Pregnant and lactating women		250 micrograms/day

Source: Data from UNICEF.

Methods of Assessment of Iodine Deficiency and Endemic Goiters

Assessment of iodine nutritional status of a population can be done by four methods (Table 3.3), namely goiter prevalence rate, UI, serum TSH, and serum thyroglobulin measurements.[7,8] These four parameters are indicative of iodine nutrition at different time frames and are complementary to each other. Urine iodine concentration is a sensitive indicator of iodine intake over recent days; serum thyroglobulin is reflective of an intermediate response (over weeks to months), whereas any change in the goiter prevalence rate reflects the changes in iodine nutritional status for long term (years). Total goiter prevalence (TGP) rate was used as the primary measure for iodine deficiency in a population until the 1990s. Urinary iodine provides a more sensitive measure of recent changes in iodine intake and is therefore currently the preferred indicator for assessing iodine nutritional status in the population and for monitoring changes following public health interventions.[9]

The ICCIDD/ WHO/ UNICEF recommend that school-based surveys of the median UI estimation from a representative sample of about 1200 children (spot urine collections from 30 sampling clusters of 40 children per cluster) can be used to classify a population's iodine status. Daily iodine intake of a population can be estimated by extrapolating UI concentrations from such surveys. The median iodine intake of an individual, and thus the spot urinary iodine concentration varies considerably from day to day. However, if sufficiently

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Table 3.3: Methods of population iodine nutritional status assessment

Monitoring indicator (units)	*Age group for assessment*	*Advantages*	*Disadvantages*
Median urinary iodine concentration (µg/l)	School-age children and pregnant women	• Spot urine specimens are easy to obtain • The most practical biochemical marker for iodine nutrition, when carried out with appropriate technology and sampling • Feasible to process large numbers of samples at low cost • Cut-off points proposed for classifying iodine nutrition into different degrees of public health significance are well established • External quality control program in place	• Assesses iodine intake only over the past few days • Meticulous laboratory practice is required to avoid contamination with iodine • A sufficiently large number of samples must be collected to allow for varying degrees of subject hydration and other biological variations among individuals • Not valuable for individual assessment
Goiter rate assessed by palpation (%)	School-age children	• Simple and rapid screening test • Requires no specialized equipment	• Specificity and sensitivity of palpation are low in grades 0 and 1 due to a high inter-observer variation • Responds slowly to changes in iodine intake
Goiter rate assessed by ultrasound (%)	School-age children	• A more precise measurement of thyroid volume compared with palpation • Safe, non-invasive • International reference values for thyroid volume in school children are available as a function of age, sex, and body surface area	• Expensive equipment and a source of electricity is needed - operator needs to be specially trained in the technique • Responds slowly to changes in iodine intake
Serum TSH (mIU/l)	Newborns	• Measures thyroid function at a vulnerable age when iodine deficiency directly affects the developing brain • If screening programs to detect congenital hypothyroidism is in place then only additional cost will be for data analysis • Collection by heel stick and storage on filter paper is simple • Blood spots can be stored for several weeks at cool, dry room temperatures	• Not recommended to be set up solely to assess community iodine deficiency due to expense • Cannot be used when antiseptics containing iodine are used during delivery • Requires use of a standardized, sensitive assay • Should be taken either from the cord at delivery or by heel prick at least 48 hours after birth to avoid physiological newborn surge
Serum Thyroglobulin (µg/l)	School-age children	• Collection by finger stick and storage on filter paper is simple • Can be stored for several weeks at cool, dry room temperatures, so sampling practical even in remote areas • Measures improving thyroid function within several months after iodine repletion • Standard reference material is now available, but needs to be validated • An international reference range has been established	• Expensive immunoassay • Requires laboratory infrastructre

Source: Data from WHO.

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Table 3.4: Epidemiological criteria for assessing iodine nutrition based on median urinary iodine levels of school going children (≥ 6 years)*

Median urinary iodine (µg/l)	*Iodine intake*	*Iodine status*
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	Likely to provide adequate intake for pregnant/ lactating women, but may pose a slight risk of more than adequate intake in the overall population
≥ 300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases)

*(Applies to adults, but not to lactating or pregnant women).
Source: Data from WHO.

large numbers of samples have been collected, iodine concentrations in morning or other spot urine samples from children or adults provide an adequate assessment of a population's iodine nutrition. Twenty-four hours urine collections are preferable for estimation of iodine intakes in individuals, but are difficult to obtain. Normalizing urinary iodine to creatinine levels, as has been done in the past, is cumbersome, expensive, and unnecessary.[9] Considering any individual with urinary iodine levels of <100 µg/L, as iodine deficient is a common mistake made by clinicians.[10] Median UI levels of 100–120 µg/L in school children are considered normal, and any values <100 µg/L are considered indicative of low iodine intake. Levels between 50 and 99 µg/L are indicative of mild iodine deficiency, 20–49 µg/L of moderate iodine deficiency, and <20 µg/L of severe iodine deficiency (Table 3.4).

TGP rate of a population has been estimated by screening school children either with clinical palpation or with ultrasonographic evaluation. The TGP rates are closely correlated with the iodine nutrition status of a population and can be used to classify the severity of IDD based on TGP rates in school age children in a population (*see* Table 3.3). Goiter is classified according to the size of the thyroid gland on inspection and palpation. The first staging

Table 3.5: Grading system of endemic goiters

Grade 0	No palpable or visible goiter
Grade 1	A mass in the neck that is consistent with an enlarged thyroid that is palpable but not visible when the neck is in the neutral position; it also moves upward in the neck as the subject swallows
Grade 2	A swelling in the neck that is visible when the neck is in a neutral position and is consistent with an enlarged thyroid when the neck is palpated.

Adopted from: Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. – 3rd ed. © World Health Organization 2007.

system proposed by WHO in 1960[11] has been replaced by a simplified grading system (Table 3.5) established by the WHO/UNICEF/ICCIDD consultation on IDD indicators in November 1992. The newer and simpler goiter classification combines the earlier stages Ia and Ib into grade 1, and combines stages II and III into grade 2.[2] The sum of grades 1 and 2 is taken as the total goiter rate. The relative simplicity of this system facilitates easy training of field staff and implementation in public health surveys. In the areas with mild endemic iodine deficiency, the TGP rates are low and goiters are generally small (i.e. grade 1 or bordering on either grade 0 or 2). Interobserver variations based on palpation-based studies in such areas can be up to 40%. Therefore, ultrasonography is recommended by the WHO as a safe, noninvasive method for providing precise and objective measurement of thyroid volume than the more subjective method of palpation.[12]

Thyroid hormones and serum thyroglobulin levels are of little value in field-based studies of iodine nutrition, and are recommended to be used only for special situations. Serum triiodothyronin (T_3) and TSH remain unchanged or show mild elevation, and serum T_4 is usually low in iodine-deficient populations. However, these values may remain within the normal range, and the overlap with iodine-sufficient populations is large enough to make thyroid hormone concentrations an insensitive measure of iodine nutrition in children and adults. However, in newborns, TSH obtained 3–4 days after birth is a sensitive indicator of iodine nutritional status. This is because compared with adults, the thyroid of a newborn contains less iodine and has a higher iodine turnover rate. As a result, when iodine stores are low, maintaining high iodine turnover requires

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Table 3.6: Insufficient iodine intake in school-age children (6–12 years) and in the general population (all age groups), by WHO region, 2007

		Insufficient iodine intake (UI < 100 µg/L)			
		School-age children		*General population*	
WHO region[a]	*Countries (no.)*	*Proportion (%)*	*Total no. (millions)*[b]	*Proportion (%)*	*Total no. (millions)*[b]
Africa	13	40.8	57.7	41.5	312.9
Americas	3	10.6	11.6	11.0	98.6
South-East Asia	0	30.3	73.1	30.0	503.6
Europe	19	52.4	38.7	52.0	459.7
Eastern Mediterranean	7	48.8	43.3	47.2	259.3
Western Pacific	5	22.7	41.6	21.2	374.7
Total	47	31.5	266.0	30.6	2,008.8

[a]193 WHO member states.
[b]Based on population estimates in the year 2006 (2004 revision).
Source: Data from WHO.

enhanced TSH stimulus. Serum TSH levels are therefore higher in iodine-deficient infants for the first few weeks of life.[13]

Current Status of Global Iodine Nutrition

Based on the current estimates, the iodine intake of 266 million (31.5%) school-age children worldwide is insufficient. As listed in Table 3.6, iodine intake is lower than the daily requirements in 73 million children living in South-East Asia and in 57.7 million children living in Africa. In European, and Eastern Mediterranean and Western Pacific regions, the figure is approximately 40 million children, whereas in the Americas, 12 million children have insufficient dietary iodine intake. The greatest proportions of children with inadequate iodine intake live in the regions of Europe (52.4%) and the Eastern Mediterranean (48.8%), and the smallest proportions reside in the Western Pacific (22.7%) and the Americas (10.6%). Due to the wide variability of iodine nutritional status across the globe, countries have been classified into six categories of public health significance with respect to the iodine intake estimated from median UI (Fig. 3.1). Iodine intake was insufficient in 47 countries, adequate in 49, more than adequate in 27, and excessive in seven according to WHO 2007 data. Of the 47 countries with insufficient intake, 10 were classified as moderately deficient and 37 as mildly deficient. No countries were categorized as severely deficient.

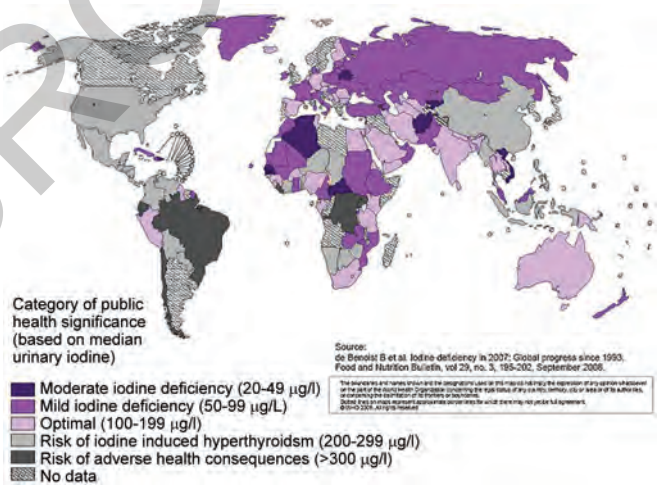

Fig. 3.1: Variable severity of iodine deficiency based on median urinary iodine (1993–2006).
Source: Data from WHO.

ETIOLOGY OF IODINE DEFICIENCY AND ENDEMIC GOITERS

The majority of the earth's natural iodine exists in the oceans in the form of iodide salts. The inland natural iodine mostly exists in the form of iodine salts in soil, almost all of which is water-soluble, and can be easily depleted by rainwater into the sea via rivers. In mountainous areas, snow, water, and glaciation leach the iodine from the soil. Lowlands can also become iodine deficient due to heavy rainfall or flooding.[14] Historically, the most prominent geographic areas with high rates of goiters have been the northern

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Table 3.7: Severity of iodine deficiency as assessed by goiter prevalence in school age children

	Degrees of IDD, expressed as percentage of the total of the number of children surveyed[a]			
Total goiter rate (TGR)	*None*	*Mild*	*Moderate*	*Severe*
	0.0–4.9%	5.0–19.9%	20.0–29.9%	≥ 30%

[a]Goiter prevalence responds slowly to changes in iodine intake.
Source: Data from WHO.

and southern slopes of the Himalayas, the Andean region of South America, the European Alps, and the mountainous areas of China. However, goiters also occur in plains and lowlands far from the oceans, such as the central part of Africa and, to a lesser extent, in the coastal areas of Europe.[15]

The thyroid hormones, namely T_4 and T_3, contain a high amount of iodine, which is an essential substrate needed for their synthesis. A healthy adult human body contains 15–20 mg of iodine, of which 70% is in the thyroid. In long-standing iodine deficiency, the iodine content of the thyroid can fall to <20 μg. The thyroid gland of an average normal human releases about 65 μg of iodine daily into the circulation, which is thus the minimum daily requirement of iodine.[8] Iodine intake is considered adequate when it is between 100 and 200 μg/day. The principal source of iodine intake is from diet or pharmaceutical supplementation.[10] Fish, seafood, and seaweed are richest source of dietary iodine, which is also found to a lesser extent in milk, eggs, and meat from animals consuming an iodine sufficient diet. With the exception of spinach, fruits and vegetables, as well as drinking water have too low iodine contents to provide for the daily iodine requirements. Food grown in iodine-deficient environment has low iodine content, thus contributing to iodine deficiency.

Iodate is a commonly consumed form of iodine in diet, and is widely used in iodization of salt. Iodate is reduced in the gut into iodide, which is rapidly and almost completely absorbed in the stomach and duodenum. The human sodium/iodide symporter (hNIS) protein facilitates active iodide uptake into the thyroid at a concentration gradient of 20–50 times that of plasma. Thyroid uptake and clearance of circulating iodine varies with iodine intake. In physiological conditions with adequate iodine supply, 10% or less of absorbed iodine is taken up by the thyroid. In conditions of chronic iodine deficiency, the thyroid uptake of absorbed iodine can exceed 80%. The physiologic iodine requirements increase during puberty, pregnancy, and lactation.

The turnover of thyroid hormones is slow, with the half-life of T_4 being about 5 days while that of T_3 being 1.5–3 days. The iodine released from thyroid re-enters the plasma iodine pool, and can be taken up again by thyroid or gets excreted by the kidney. More than 90% of ingested iodine is ultimately excreted in the urine. While dietary iodine deficiency is the main cause of endemic goiters, other dietary substances that are called goitrogens can interfere with thyroid metabolism, and result in goiters.[16–19] Most goitrogens do not have discernable manifestations by themselves, and cause goiters only in presence of coexisting iodine deficiency.

Low supply of dietary iodine is the main cause of endemic goiter. Severity of iodine deficiency can be assessed based on the goiter prevalence in school-age children (Table 3.7). Increasing iodine consumption in endemic iodine-deficient regions has brought down the goiter prevalence rates. However, some areas have seen persistence of goiters despite adequate iodine supplementation, which is attributed to the existence of other goitrogenic factors. Vegetables of the Brassica family, including cabbage and turnips contain natural goitrogens, which have antithyroid action due to the thioglucosides, which release thiocyanate and isothiocyanate. These compounds have goitrogenic effect by inhibiting iodide transport certain Cruciferae growing as in the thyroid gland. Goitrin, a thioglucoside, is found in weeds found in Finland and Tasmania.[20] Cyanoglucosides, other naturally occurring goitrogens, are found in certain staple foods of the tropics, such as cassava, maize, bamboo shoots, and sweet potatoes, and are converted to thiocyanate after digestion. Millet, a staple food in Sudan, contains flavonoids, which too is known to have antithyroid activity by impairing thyroid peroxidase.[21] Protein malnutrition coexists frequently with endemic goiter, and has been shown to have a goitrogenic effect in endemic areas due to alterations in thyroid morphology and functions.[22]

PATHOPHYSIOLOGY OF ENDEMIC GOITER

Formation of endemic goiter is the net result of a cascade of physiologic and morphologic changes that occur in the

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thyroid gland as an adaptation to dietary iodine deficiency. Thyroid hormone synthesis is impaired due to low dietary iodine intake, which leads to increased thyroidal iodide clearance from the plasma and decreased urinary iodine excretion, in an attempt to conserve iodine. T_3 is three to four times more potent than T_4, but contains only three fourths as much iodine as T_4. Relative proportion of T_3 rises due to its preferential synthesis over T_4, and increased peripheral conversion of T_4 to T_3.[23] As a result, clinical euthyroidism is maintained, but biochemically the pattern of low serum T_4, elevated TSH, and normal or elevated T_3 is often found.[24–26] Serum T_3 and T_4 levels are low and serum TSH levels markedly elevated in severe thyroid failure, such as that in endemic cretinism. But in the majority of cases, the hypothyroidism is less severe, and result in serum T_3 and T_4 levels remaining normal, with normal or moderately elevated serum TSH levels. There may be an exaggerated TSH response to thyrotropin-releasing hormone (TRH) stimulation, which reflects increased pituitary reserve of TSH and subclinical hypothyroidism.

In addition to known effect of iodine deficiency resulting in compensatory growth of the thyroid gland to synthesize thyroid hormone, goiter formation has been proposed to be a direct consequence of elevation in serum TSH levels. However, the goiter size and serum TSH levels are not entirely correlated, and a wide variation in the level of TSH is observed in normal and goitrous individuals in endemic areas.[27] This lack of correlation between goiter size and thyroid hormone levels suggests the possible role of circulating thyroid growth factors, such as epidermal growth factors, or an autoimmune process in the pathogenesis of goiter.[28] Thyroid growth-promoting immunoglobulin (TGI) has been implicated in initiation and progression of sporadic and endemic goiters by some,[29] but this has been contested by other investigators due to conflicting results, and questionable methods of detection TGI.[30–32]

Various genetic and environmental factors, female gender, old age, and smoking have been associated with goiter formation, and the occurrence and severity of IDD and endemic goiters. Smoking is a major source of thiocyanate in human beings and has been shown to cause reduced breast milk iodine content in infants being breast fed by women who smoke. Most familial goiters in endemic as well as nonendemic regions present an autosomal-dominant pattern of inheritance. In contrast, sporadic goiters are characteristically linked to recessive genomic variation. Gene–gene interactions of various polygenic mechanisms possibly explain the complex pathogenesis of goiters, and offer an explanation for their genetic heterogeneity. Children from parents with goiter have a significantly higher risk of developing goiter compared with children of nongoitrous parents. Genome-wide association studies have identified several candidate loci including *MNG1* on chromosome 14q31, and a region on 14q31 between *MNG1* and *TSHR* genes. Numerous other putative polymorphisms, including X-linked autosomal-dominant linkage to a locus on chromosome Xp22 (*MNG2*), and thyroglobulin have been identified in families with goiters. It is possible that a synergistic effect of several weak genetic variations in different genomic regions leads to goiter predisposition.[33]

MORPHOLOGIC CHANGES IN ENDEMIC GOITER

The physiologic response to iodine deficiency usually results in increased functional activity of thyrocytes and hyperplasia with increase thyroid gland mass. Initially, iodine deficiency causes diffuse thyroid hyperplasia with cellular hypertrophy and reduction in follicular spaces due to excess secretion of TSH in an effort to maximize availability of iodine, leading to a diffuse goiter (Fig. 3.2). In chronic iodine deficiency, the follicles become inactive and distended with colloid accumulation. These changes persist into adult life, and focal nodular hyperplasia may develop, leading to nodule formation. Nearly all goiters become nodular with time. Nodularity is believed to be a result of the waxing and waning TSH levels that cause areas of nodular hyperplasia and involution, interspersed with areas of necrosis and colloid filled cysts separated by fibrous septae. Some nodules retain the ability to secrete thyroid hormone and are seen as hot nodules on radionuclide scan. Others do not retain this ability, become inactive, and form cold nodules.

Thyroid hormone synthesis requires H_2O_2 production and free radical formation, which may damage genomic DNA and cause mutations. High spontaneous mutation rate and a high replication rate are associated with failure of mutation repair and an accumulation of mutations in the thyrocytes. Some spontaneous mutations confer constitutive activation of the cyclic adenosine monophosphate (cAMP) cascade[34] (e.g. *TSHR* and Gs α mutations)

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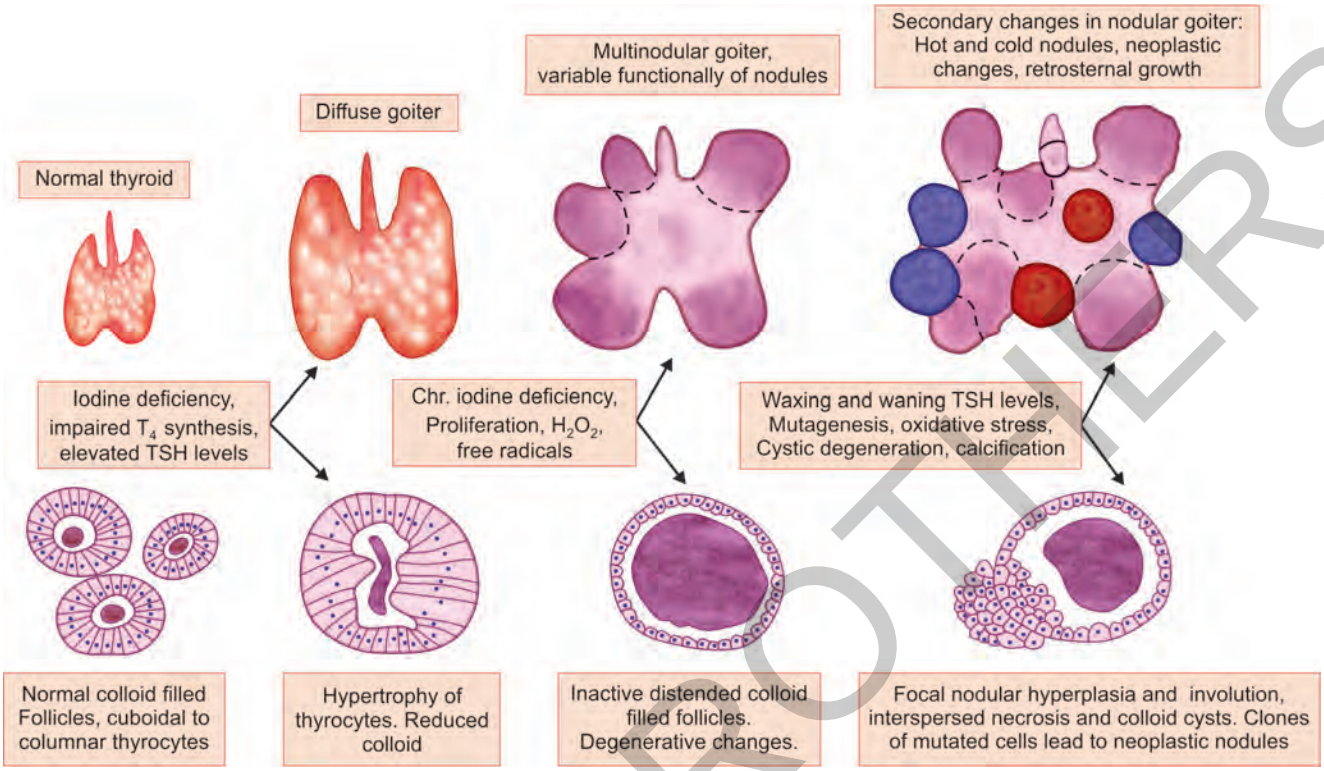

Fig. 3.2: Pathophysiology of endemic goiter and morphological changes in thyroid gland.

that stimulates growth and function. Growth factor expression (e.g. insulin-like growth factor-1 [IGF-I], transforming growth factor [TGF]-ß1, or epidermal growth factor [EGF]) may also be increased or have more potent effect on activated intracellular mitogen signaling pathways. As a result, most cells divide and form small clones. Once the high growth factor expression ceases, small clones of cells with activating mutations can further proliferate and have uncontrolled cellular proliferation (Fig. 3.2). Unhindered growth of such clones of cells with activating mutations, along with cystic necrosis and scarring in turn can result in the formation of benign or malignant thyroid nodules.[35]

ASSESSMENT AND DIAGNOSIS OF ENDEMIC GOITERS

In epidemiological studies, when palpation is used for goiter assessment, an individual is considered as having a goiter when each thyroid lobe has a volume greater than the terminal phalanx of the thumb of the individual being examined.[7] However, this crude method has very low sensitivity and specificity. Measurement of thyroid volume by ultrasound is preferable for the classification of goiter. In clinics, endemic iodine deficiency goiters—diffuse or nodular—present with similar clinical and biochemical manifestations as sporadic multinodular goiters, and can result in similar symptoms and secondary changes including thyrotoxicosis and malignant transformation. The clinical, biochemical, and imaging evaluation of multinodular goiters are described in greater details in other chapters of this book. Few features typical to endemic goiters are described below.

Most children have a diffuse thyroid enlargement or diffuse goiter, which may turn nodular at a young age. Only few diffuse goiters persist till adulthood (Fig. 3.3). The main bulk of the goiter is replaced by multiple nodules that form a MNG on palpation in endemic regions. Severe iodine deficiency may result in endemic cretinism—a dreaded sequel that is easily preventable with iodine prophylaxis but is not curable once it has occurred. Maternal T_4 and dietary iodine deficiencies may retard the intrauterine growth of the fetus. As a result, the infant may be born with mental retardation and either a predominantly neurological syndrome of hearing and speech defects associated with

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Fig. 3.3: Diffuse euthyroid goiter in an adult.

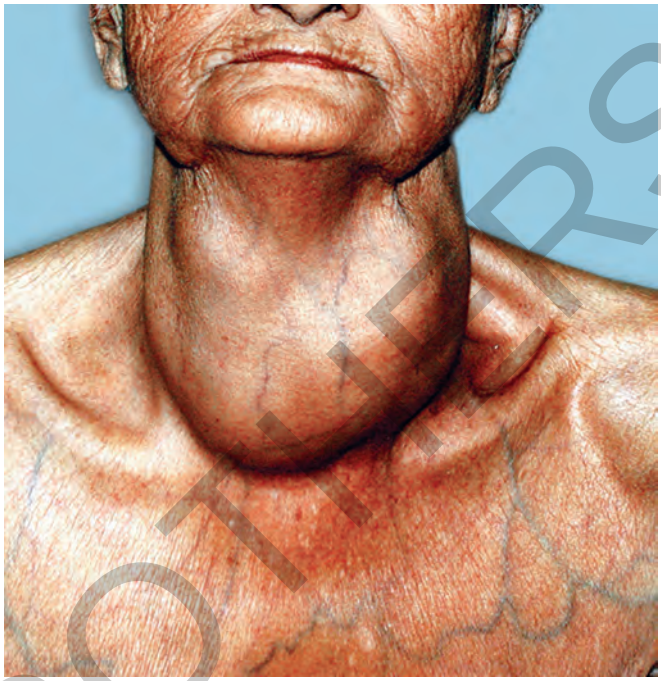

Fig. 3.4: Large goiter with thoracic inlet obstruction.

varying degrees of characteristic stance and gait disorders[36] or predominant hypothyroidism and stunted growth.[14] Unless treated at the stage of diffuse goiters or an early phase of multinodularity, the goiters usually progress and may attain large size. Mechanical problems often arise in patients with huge goiters that cause tracheal deviation and compression. Large, substernal, or retrosternal goiter can cause venous obstruction and the development of collateral venous circulation on the chest wall (Fig. 3.4), which mandates a surgical intervention. The presence of hard or calcified nodules suggests possible malignant disease. Despite biochemical picture of hypothyroidism, with low or low-normal serum T_4 concentrations and minimally elevated serum TSH levels, most patients do not have clinical manifestations of hypothyroidism.

Some nodules may gain autonomy, resulting in failure of ^{131}I or ^{123}I suppression with T_3 and absence of TSH response to TRH. Hyperthyroidism in older patients with endemic goiter may be precipitated by iodination and cause Jod–Basedow hyperthyroidism or may be the result of secondary hyperthyroidism in MNG.[37] Scintigraphy of the thyroid in endemic areas may show marked heterogeneity in the uptake of radioiodine and formation of hot or cold nodules. Similar to sporadic goiters, ultrasonography is currently the mainstay of imaging diagnosis in patients with endemic goiters. Ultrasonography with color Doppler studies make characterization of thyroid nodule(s) possible, detection of neck nodes, and helps select suspicious lesions for fine-needle aspiration cytology (FNAC), which is an important component of assessment of any nodular goiter. Long-standing goiters may show dystrophic calcifications mostly seen along nodule walls (Fig. 3.5A). In patients with suspicion of retrosternal extension or invasive thyroid cancer, a contrast enhanced computed tomography (CT) scan (Figs. 3.5B and C) or magnetic resonance imaging (MRI) may be helpful. Whether or not the incidence or prevalence of thyroid cancers is higher in endemic iodine-deficient regions remains controversial.[38,39] Follicular and anaplastic carcinomas are relatively more common in areas of endemic goiter, yet papillary thyroid cancer is the most common histological type. The diagnosis is often delayed in such patients because goiters are so common in iodine-deficient areas. FNAC helps select patients for total or near-total thyroidectomy (NTTx).[40] Some other controversial issues include higher incidence of poor-prognostic variants of differentiated thyroid cancers such as tall cell or insular variants and worse prognosis of thyroid cancer in endemic goiters.[41]

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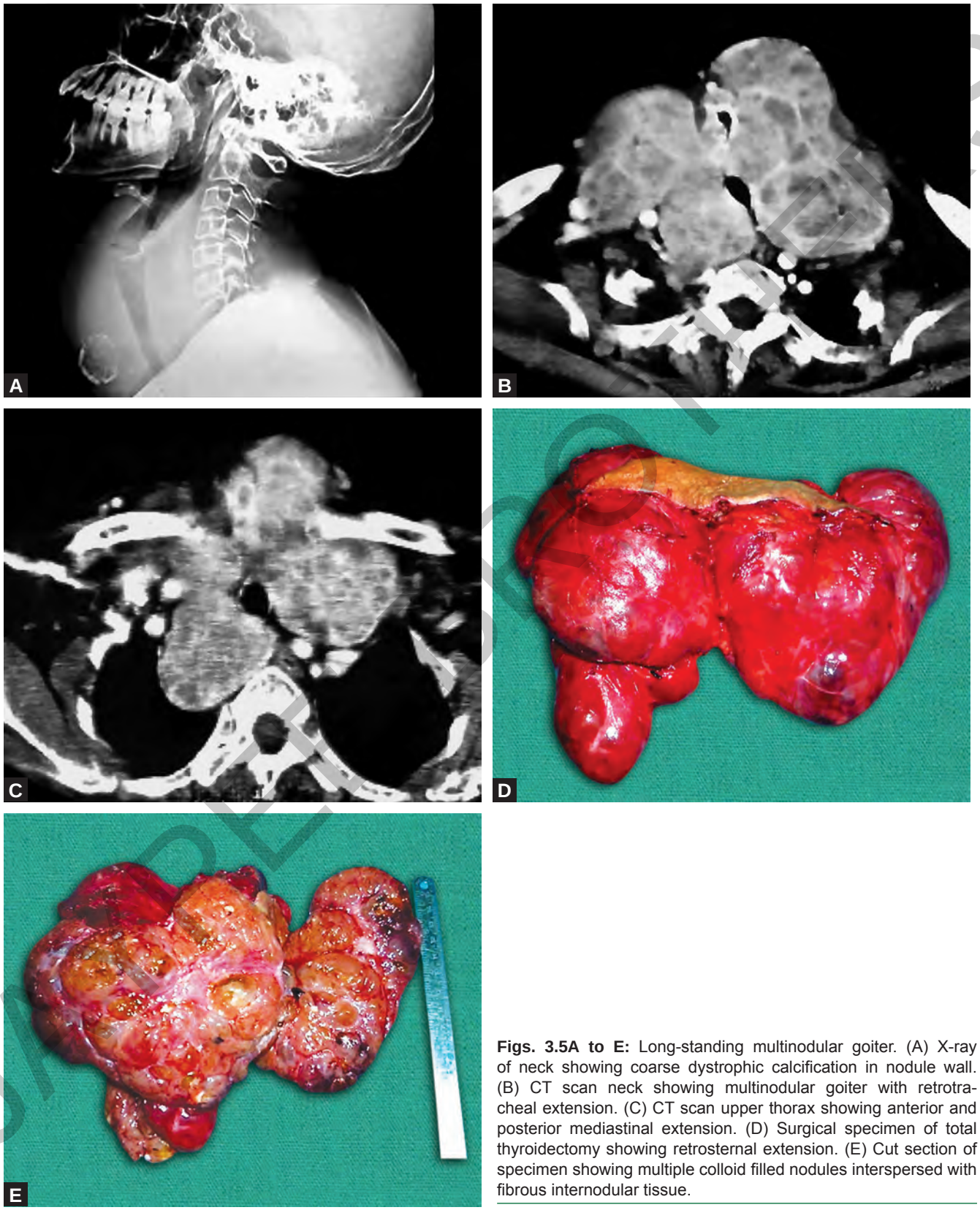

Figs. 3.5A to E: Long-standing multinodular goiter. (A) X-ray of neck showing coarse dystrophic calcification in nodule wall. (B) CT scan neck showing multinodular goiter with retrotracheal extension. (C) CT scan upper thorax showing anterior and posterior mediastinal extension. (D) Surgical specimen of total thyroidectomy showing retrosternal extension. (E) Cut section of specimen showing multiple colloid filled nodules interspersed with fibrous internodular tissue.

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PROPHYLAXIS AND CONTROL OF IODINE DEFICIENCY AND ENDEMIC GOITERS

The occurrence of endemic goiter can be prevented by supplying an adequate amount of iodine in the diet and eliminating goitrogens and malnutrition. Adequate dietary iodine intake is vital in specific vulnerable groups, such as infants and pregnant or lactating women.[8] The most logical and effective strategy for IDD control and prevention of endemic goiters is to increase iodine intake through supplementation or food fortification, and surveillance and monitoring of iodine nutritional status. Advocacy to mobilize public health authorities and educate the public are vital in achieving this goal on a long-term basis. Table salt is a commodity almost universally used in diet and is the most commonly used approach for iodine supplementation. The World Health Assembly in 1992 adopted USI for iodization of salt for both human and livestock consumption as the method of choice to eliminate IDD. Iodization of salt does not affect its color, taste, or odor. Technology for iodization of salt is easy and inexpensive. Besides, salt is produced and distributed through few entities, thus making monitoring the quality of iodized salt at the production, retail and household levels relatively easy. Compared to other methods of iodine supplementation, salt iodization programs are easier and cheaper to implement. Assuming an average salt intake of 10 g per person/day, the daily recommended intake of iodine can be met by adding 20–40 ppm of iodine to salt.[7] Potassium iodate is preferred over potassium iodide for iodine fortification of salt as iodate is more stable under various climatic conditions, especially in hot and humid climates.[7] Other sources of dietary iodine are milk, eggs, fish and other seafood. Other vehicles for iodine supplementation include drinking or irrigation water, milk, bread, and cattle feed.[42–46] Iodine administration in the form of KI (30 mg/month or 8 mg/2 weeks) or potassium iodate drops or tablets is another option. Yet another option for iodine supplementation is an intramuscular injection of iodized oil containing 480 mg iodine, primarily intended for children and young or pregnant women,[3,47,48] which is sufficient for up to 3 years. Orally administered iodized oil has the advantage of avoiding injections, but has shorter and variable duration of action.[38]

GLOBAL IODIZATION PROGRAMS AND THEIR EFFECT ON IODINE DEFICIENCY AND ENDEMIC GOITERS PREVENTION AND CONTROL

The current picture of global iodine nutritional status is much better compared to what it was about a decade ago. This improvement in iodine nutrition has largely resulted from the concerted efforts of a coalition of international organizations including the ICCIDD, WHO, Micronutrient Initiative, and UNICEF, and their collaboration with national IDDs control committees of various countries and the salt industry.[8] Universal salt iodization program is an effective public health strategy for reducing iodine deficiency in a population. Before initiation of the USI and iodine supplementation programs, the main parameters used as indicators of IDD status were goiter size and urinary iodine levels. Other factors like cretinism, neonatal TSH, and thyroglobulin levels were also used. Since the time iodine supplementation programs have been implemented, iodized salt consumption rates and median UI excretion are taken as the main indicators of IDD status, while goiter prevalence or size and neonatal TSH levels are also used at times.

As a result of these efforts, globally, the number of households using iodized salt has risen from <20% before 1999 to >70% in 2007, thus reducing iodine deficiency substantially. The number of countries with iodine deficiency has decreased from 110 in 1993 (using TGP as indicator) to 54 in 2003 and 47 in 2007 (using UI as indicator).[4] Although the ambitious goal of IDD elimination set by the coalition of ICCIDD, WHO, and UNICEF could not be achieved by year 2000, the global progress in reducing iodine deficiency has been impressive. Data from all WHO regions, as well as the worldwide data suggest substantial reduction in proportion of school children at risk of iodine deficiency, as estimated by improved median UI concentrations between 2003 and 2007 (Fig. 3.6). Some 36 of the world's poorest countries have achieved salt iodization targets; yet in 38 countries, less than half of the population has access to iodized salt as per 2007 WHO data. Countries such as the United States, the United Kingdom, New Zealand, Australia, the Netherlands, Norway, and Sweden have completely eliminated IDDs.[8] Currently, the prevalence of iodine deficiency is lowest in the Americas (10·6%), where the proportion of households consuming iodized salt is the

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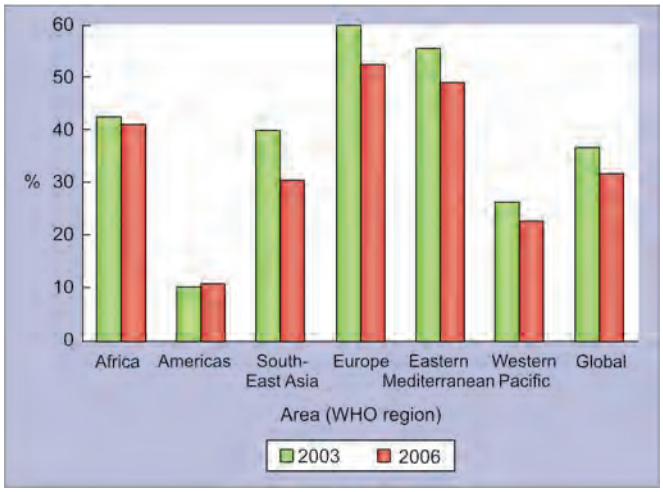

Fig. 3.6: Change in prevalence of individuals with insufficient iodine intake between the years 2003 and 2006.
Source: Data from WHO.

highest in the world (about 90%). The highest prevalence of iodine deficiency is in Europe (52%), where the household coverage with iodized salt is the lowest (about 25%).[8] Many European countries, especially in the eastern and central Europe and the countries in confederation of independent states have weak or nonexistent iodization programs. With the improved iodine nutritional status of populations, an estimated 85 million newborns out of about 130 million annual births are protected every year from impairment of learning ability. This is likely to help them achieve their genetic intellectual potential and attain educational and social development ambitions that otherwise might not have been possible had iodine deficiency persisted.

The USI and thus increased iodine intake of populations have resulted in some concerns of iodine excess in certain countries, and derangements of thyroid functions. In 2007, iodine intake was reported to be excessive, with a median UI levels >200 µg/L in 34 countries (an increase from 29 countries in 2003). Iodine-induced hyperthyroidism is related to the severity of iodine deficiency, age, duration of thyroid enlargement along with rapid increase in iodine uptake.[43,44] This increase was observed in Tasmania after bread iodination in 1966 and was most evident in older people.[45] Overall, however, the long-term correction of iodine deficiency not only abolishes endemic goiter but also reduces the incidence of toxic nodular goiters. Therefore, the occurrence of thyrotoxicosis does not outweigh the enormous benefits of iodine prophylaxis in endemic regions. Another possible concern of iodization is the rise in incidence of papillary thyroid cancer. This could also be related to other factors, e.g. radiation fallout, inclusion of papillary microcarcinomas, better access to medical care, and other unknown factors.[46,47]

MEDICAL TREATMENT OF ENDEMIC GOITERS

Efficacy of medical treatment of the endemic goiters varies widely. While treatment for a diffuse goiter can effectively reduce the size of goiter, once multinodularity has evolved and well-formed, medical treatment has limited efficacy. The treatment of multinodular endemic goiters is similar to sporadic MNGs, and is described in greater details in other chapters of this book. The non-operative treatment options for endemic goiters are iodine supplementation, levothyroxine treatment, and RAI therapy.

Iodine Supplementation

Iodine supplementation can effectively reduce the goiter volume in most patients with diffuse goiters. The limited data available on efficacy of iodine supplementation in treatment of MNGs suggest it to be no better than LT_4 therapy. In a controlled trial performed in an iodine-deficient area, a daily dose of 400 mg iodine given over 8 months was as effective as 150 µg of LT_4 in reducing the size of endemic goiter in a patient cohort of predominantly diffuse goiters.[48] The possible adverse effects of iodine supplementation include the potential to induce thyrotoxicosis in predisposed individuals due to a sudden increase in the iodine concentration. Besides, concerns of higher incidence of lymphocytic thyroiditis and papillary thyroid cancers following iodine supplementation in pre-existing endemic goiters exist and limit its use.[39] As a result, iodine supplementation is not used as treatment for endemic goiters in North America and in most European countries, with the exception of Germany.

Levothyroxine

TSH is believed to be the major growth factor for thyroid epithelial cells, resulting in formation and progression of diffuse and nodular endemic goiters.[49,50] As a result, suppression of TSH with suppressive doses of LT_4 has long been used to for treatment of diffuse as well as nodular goiters in the European countries, the United States, and Latin American countries.[49,50] While the American Thyroid Association (ATA) guidelines do not recommend LT_4 treatment as a routine for most nodular goiters, these do

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