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GOITRE: A COMPLETE REVIEW

BISWA BHUSAN MOHANTY *[1], DIVYA AGRAWAL [2], KARMAJEET RATH [3], SANJAY KUMAR [4] AND DHIRENDRA KUMAR ROY [5]

[1]Asst. Prof., Dept. of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[2]Asst. Prof., Dept. of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[3]Asst. Prof., Dept. of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[4]Associate Professor, Dept. of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[5] Professor, Dept. of Surgery, IMS & SUM Hospital, SOA University, Bhubaneswar, India

ABSTRACT

A goitre is an enlarged thyroid gland. The most common cause of goitre is lack of iodine in the diet. Hypothyroidism, hyperthyroidism, thyroid nodules or inflammation of thyroid and cancers cause goitre. Iodine is an essential micronutrient required for structural development and optimal functional activity of thyroid gland and CNS. Iodine deficiency has been shown to be associated with endemic cretinism, endemic goitre and mental retardation. Endemic goitre continues to be prevalent in the entire world. Although its etiology is complex, its prevention can be simply and effectively achieved by increasing iodine intake of the population. The best way of ensuring a continuous supply of iodine is by iodination of salt.

KEY WORDS : Goitre, thyroid gland, iodine, endemic, prevention.

BISWA BHUSAN MOHANTY
Asst. Prof., Dept. of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India

***Corresponding author**

INTRODUCTION

Iodine deficiency disorder (IDD) is the collective name of endemic goitre and endemic cretinism. It is a major worldwide problem, especially during pregnancy and childhood [1]. It is a threat to the social and economic development of countries. The most devastating outcomes of IDD are increased perinatal mortality and mental retardation. Iodine deficiency is the main preventable cause of brain damage in children and constitutes a universal public health concern [2]. This was the primary motivation in the current worldwide drive to eliminate IDD [3]. Although cretinism is the most extreme manifestation, the more subtle degrees of mental impairment leading to poor school performance, reduced intellectual activity and impaired work capacity are considerable greater significance [3, 4]. Estimates suggest that 2 billion people globally have insufficient iodine intake according to data coated from the WHO Global Database on Iodine Deficiency, 2004 by Anderson et al [3]. Goitre is conveniently referred to as endemic when it occurs in more than 10% of the population in a defined area [5]. It is the chief consequence of iodine deficiency, resulting from either low iodine intake or ingestion of goitrogens. A total goitre rate (TGR) of 5% or more is now recommended as the cut-off point to indicate a public health problem as per the decision made by the key international bodies concerned (UNICEF/ICCIDD/WHO, 1992). This recommendation is based on the observation that goitre prevalence rates between 5% and 10% may be associated with a range of abnormalities including inadequate urinary iodine (UI) excretion or subnormal levels among adults, children and neonates [6]. WHO recommends that iodine deficiency surveys should include school-age children (6-12 years) because of their high physiologic vulnerability and their accessibility through school for studies in baseline health parameters[7]. The WHO cut-off points applied for classifying iodine nutrition into different degrees of public health significance are shown in Table 1:

Table 1
Epidemiological criteria for assessing iodine nutrition based on median UI concentrations in school-age children

Median UI(µg)	Iodine intake	Iodine nutrition
<20	Insufficient	Severe iodine deficiency
20-49	insufficient	Moderate iodine deficiency
50-99	insufficient	Mild iodine deficiency
100-199	Adequate	Optimal iodine nutrition
200-299	More than adequate	Risk of iodine-induced hyperthyroidism within 5 - 10 years following introduction of iodized salt in susceptible groups
=300	Excessive	Risk of adverse health consequences (iodine induced hyperthyroidism, auto-immune thyroid diseases)

Source: WHO Global Database on Iodine Deficiency

CURRENT STATUS

Data on urinary iodine (UI) collected between 1993 and 2003 by the WHO Global Database on Iodine Deficiency were available from 126 countries of the 192 member states. Sixty-six have no data on UI. In 54 countries the population has insufficient iodine intake as indicated by a median UI below 100 micrograms/l. The lowest prevalence of iodine deficiency is found in the American

Region, where 90% of households consume iodized salt, the highest in the world. In contrast the highest prevalence of iodine deficiency is in the European Region where only 27% of households consume iodized salt [3]. Some authorities in this region have been reluctant to implement the salt iodization policy due to perceived or real complications of iodine administration [8].

During the same period data on total goitre prevalence (TGP) were available from 100 countries. Globally, the TGP in the general population is estimated to be 15.8%, varying between 4.7% in the Americas to 28.3% in Africa. When comparing current levels to the 1993 estimates, TGP has increased by 31.7% worldwide. This is inconsistent with current iodine status based on UI. Several explanations have been suggested including time lag from implementation of salt iodization programs, and poor assessment methods of TGP by palpation. The introduction of ultrasonography in recent years has increased the TGR detection when compared to initial surveys done by palpation only [3, 9]. A total of 36.5 % (285 million) school-age children were estimated to have an insufficient iodine intake. Iodine intake was more than adequate or excessive in 29 countries [3].

The world's natural supply of iodine is mostly from the ocean in the form of iodide. The commonly quoted historical areas of goitre include the Himalayan slopes, the Andean region of South America, the European Alps and the mountainous areas of China. The Rift valley regions of East and Central Africa are also endemic areas. Low lands with heavy rains or floods are usually prone to iodine deficiency.

Despite the established benefits of iodine supplementation in the prevention of endemic goitre, IDD is still a major problem in developing countries [10, 11]. The geographic isolation and the socioeconomic, cultural, and political factors in these communities contribute to the technical difficulty in implementing iodine prophylaxis programs [12]. To be successful, control programs for iodine deficiency disorders also need assessment of the salt trade, monitoring, education and occasional targeted interventions with iodized oil or other supplements [13, 14, 15].

In severely iodine deficient areas, goitre appears at an early age, and the prevalence increases markedly during childhood and attains its peak at puberty. From the age of 10 years, the prevalence is higher in girls than in boys [16], probably because of the difference in metabolism of iodine during adolescent growth. In both sexes, goitre prevalence decreases during adulthood but the decline is sharper in men than in women [17].

Endemic goitre is a problem of public health importance in India. The World's classic and most intense endemic belt runs along the southern slopes in the Himalayas extending from J & K in the West to Arunachal Pradesh, Nagaland and Manipur in the East. In addition, isolated pockets of endemicity exist in Chhota Nagpur Plateau, Arawali Range, Eastern and Western Ghats. About 40-45 million people are suffering from the disease [18]. According to a recent estimate made by the National Goitre Control Programme, Ministry of Health, Government of India, approximately 300 million people (50 percent of India's total population) are exposed to the risk of goitre throughout the country and over 60 million are goitrous [19]. Though, Delhi and its surrounding areas are located in close geographical proximity with the sub-Himalayan endemic goitre belt, as yet, there is no evidence in literature to suggest that goitre is prevalent in endemic proportions in these areas.

DEFINITIONS OF SIMPLE AND ENDEMIC GOITRE:

CRITERIA FOR ENDEMICITY:

Simple goitre: Anatomical enlargement of the thyroid gland without a functional alteration is called euthyroid or simple goitre. By convention it is regarded as a compensator phenomenon which results when a single or a combination of factors interferes with the optimal formation of the hormones of the thyroid gland. In fact, the

term “simple goitre” was used by Wane, Koutros and Alexander (1964) to denote those cases of nontoxic goitre where they could not find an evidence of factors like dyshormongenesis, autoimmune thyroiditis or ingestion of goitrogens [20].

Endemic goitre: The prevalence of enlargement of the thyroid gland occurring in more than 10% of people living in any circumscribed area is called endemic goitre.

Criteria for Endemicity: Cases of enlargement of thyroid gland are found in all Communities; even when there is an ample supply of iodine in the diet. Hence certain criteria have to be satisfied before designating an area as being endemic for goitre.

Classification

Main classifications have been suggested for field use in assessing the prevalence of thyroid enlargement. The scheme adapted by Stanbury and his colleagues [21] and those suggested by Perez et al [22] is more accepted:

Grade 0a: Thyroid not palpable, or if palpable not larger than normal.

Grade 0b: Thyroid distinctly palpable but not visible with the head in a normal or raised portion considered to be definitely larger than normal, i.e. at least as large as the distal phalanx of the subject’s thumb.

Grade I: Thyroid easily palpable and visible with the head in either a normal or a raised position. The presence of a discrete nodule qualifies a patient for inclusion in this grade.

Grade II: Thyroid easily visible with the head in a normal position.

Grade III: Goitre visible at a distance.

Grade IV: Monstrous goitres.

Epidemiological Criteria: Endemic goitre would be considered to exist.

(a) When more than 5 per cent of an adolescent or pre-adolescent group has ‘grade I’ goitre or,

(b) When more than 30 per cent are assigned to ‘grade 0b’ or above.

This decision would be reinforced if it could be shown that in a fair sample of the population the mean daily excretion of iodine in the urine is:

(a) Less than 50 µg per 24 hours, or

(b) Less than 50 µg per gram of creatinine, in randomly obtained specimens.

NATURAL HISTORY AND PATHOPHYSIOLOGY

The thyroid gland makes and releases two small chemicals into blood called thyroid hormones i.e. triiodothyronine (T3) and tetraiodothyronine (T4). Each of them is comprised of a pair of connected tyrosine amino acids to which three or four iodine molecules attached respectively. The iodine needed for thyroid hormone production comes from our diet in sea food, dairy products, store bought bread and iodized salt. Once absorbed, iodine in the blood is trapped by a special pump in thyroid cells, called the sodium iodide importer. The thyroid also has several specialized biochemical fastening machines called as enzymes that then carry out the steps needed to attach iodine to particular parts of a very big protein called thyroglobulin, which is made only by thyroid cells. Some of this thyroglobulin with iodine molecules attached is stored in the gland in the form of a paste called colloid. It is usually stored in the center of the follicles.

A regulated amount of the thyroid hormone is constantly being chopped off of thyroglobulin and secreted into blood for delivery to tissues throughout the body. In the nucleus of almost every cell, thyroid hormones bind to the molecules called T3 receptors, which are attached to the segments of DNA that regulate certain genes. Precise control of how many proteins are made from these genetic blueprints maintains the normal euthyroid state. Excessive activation of these genes by abnormal high thyroid hormone levels causes hyperthyroidism; inadequate gene activation due to insufficient thyroid hormone production causes hypothyroidism. Thyroid gland makes precisely the right amount of its

hormones under control of the pituitary gland. Specialized pituitary cells make thyroid stimulating hormone (TSH), which travels in blood to the thyroid gland, where TSH binds to its own receptors on thyroid cells, promoting them to grow and produce more of the thyroid hormones. Usually, this system is kept in balance by the negative feedback of the thyroid hormones on TSH- secreting pituitary cells (as well as the part of the brain that controls them) (Figure 1).

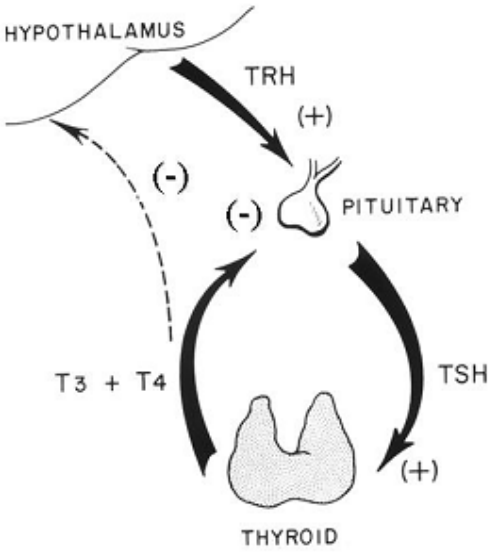

Figure 1
Hypothalamic control on Thyroid gland

CAUSES OF GOITRE

Three categories of problems are responsible for almost all causes of thyroid gland enlargement i.e. insufficient thyroid hormone production, gland inflammation and tumors of the gland.

When the gland is not capable of making sufficient amount of thyroid hormone, it compensates by getting bigger. Worldwide the most common cause is dietary iodine deficiency, a condition estimated still to affect 100 million people who live in poverty stricken societies. Iodine is an essential building block for thyroid hormones; in the absence of adequate supply, the gland becomes larger. When more than 10% of a population has goitre due to iodine deficiency, it is called as endemic goitre. In endemic areas, a wide variation in the level of TSH has been observed in normal and goitrous individuals. Such dissociation between goitre size and biochemical findings suggests the possible role of circulating thyroid growth factors, such as epidermal growth factors, or an autoimmune process in the pathogenesis of goitre [23].

Other consequences of severe iodine deficiency include hypothyroidism and cretinism, a syndrome of mental retardation, short stature, deafness and characteristic facial deformities that affects children born to hypothyroid mothers in iodine deficient regions. Generalized epithelial hyperplasia occurs, with cellular hypertrophy and reduction in follicular spaces. In chronic iodine deficiency, the follicles become inactive and distended with colloid accumulation. These changes persist into adulthood, and focal nodular hyperplasia may develop, leading to nodular formation. Some of these nodules retain the ability to secrete thyroxine and form functioning thyroid nodules [24]. Others do not retain this ability, become inactive and form cold nodules. Necrosis and scarring result in fibrous septae, which contribute to the formation of

multinodular goitre [25]. People with defects in their genetic blueprints for the proteins that permit the thyroid gland to make thyroid hormone (e.g. mutation in the molecular pump that enables the thyroid to concentrate iodine within itself) typically develop a goitre. Certain drugs can also interfere with normal thyroid function and lead to compensator gland enlargement such as lithium carbonate, which causes goitre in 10% of individuals taking this medicine. Other drugs include methimazole, minocycline, propylthiouracil, thiomides, thioureylene. The chronic shortage of iodine in the diet is the worldwide most common cause for an enlarged thyroid.

Inflammation of the thyroid gland (*thyroiditis*) can produce gland swelling. Some forms of thyroid inflammation are quite common, such as autoimmune thyroiditis and painless (postpartum) thyroiditis. Autoimmune thyroiditis (also called Hashimoto thyroiditis) occurs when a person's immune system turns against their own thyroid gland, inflaming it, usually causing the gland to swell, and often making it permanently underactive. Autoimmune thyroiditis can first appear in children and young adults, but its incidence increases sharply in middle aged and elderly people.

Other types of thyroiditis causing goitre include:

1. Painless (postpartum) thyroiditis, a self-limited inflammation of the thyroid that can resolve without treatment and affects at least 5% of women in the year after pregnancy;
2. Subacute thyroiditis, which causes painful thyroid enlargement as the result of viral infection.
3. Other rarer forms of infectious thyroiditis.
4. Drug-induced thyroiditis, such as those caused by amiodarone and interferon α
5. A rare fibrosing condition called Reidel thyroiditis.

Third, goitre can be the result of thyroid tumors, which are usually benign, but sometimes malignant. Most thyroid tumors present as discrete nodules, but there are several kinds of thyroid cancer that can cause generalized swelling of the gland. These include infiltrating papillary thyroid cancer, lymphoma and anaplastic thyroid cancer. Certain facts make it important to consider the possibility that a goitre might be malignant. These include one or more of the following symptoms: rapid enlargement of a goitre over a few weeks, the onset of new thyroid-related pain, difficulty swallowing, shortness of breath, or coughing up blood; or a goitre in someone with risk factors for thyroid cancer, such as a person who had childhood radiation to their neck or who has a close relative with thyroid cancer.

GOITROGENS

(1) Lack of iodine is the number one cause of a goitre. The body needs iodine to make the T4 molecule. The solution to this problem is to supplement the diet with iodine and the seaweed called bladder wrack is one of the best sources of available iodine. The herb, Ashwagandha, has been shown to help increase T4 levels.

(2) Heavy metals such as lead, mercury, and cadmium, suppress the enzyme that converts inactive T4 to active T3. Bladder wrack helps to remove heavy metals from the body.

(3) Selenium deficiency can prevent the body from making T3 because selenium is necessary in the process of converting the hormone T4 to T3. Selenium is also used in the process of removing used hormones from the body. It is also an antioxidant, an anti-cancer agent. It removes heavy metals from the body and aids in the prevention of heart disease. Two things that cause selenium depletion are mercury amalgam dental fillings, and a liver that is struggling with toxicity. The result is the body's decreased ability to convert T4 to active T3. The pituitary will sense this lack of T3 and release TSH telling the thyroid to make more T4. As mentioned above, this can back up the system and cause a goitre.

(4) Stress, physical or emotional, can have an adverse effect on the thyroid through a secondary problem caused by the adrenal glands releasing cortisol. Cortisol also suppresses the conversion of T4 to T3. The solutions for this include anything that reduces stress in your life, such as:

(a) Getting plenty of sleep

(b) Scheduling down time, fun time, and alone time, and

(c) Joining either a yoga, meditation or Tai Chi class.

If a person has been under stress for an extended amount of time, he might need adrenal support. Another herb that has been shown to assist with the T4 to T3 conversion process is Guggul Gum. This herb is found to lower cholesterol as well.

(5) Another way that lack of selenium or increased cortisols affect thyroid function is that while they both suppress T4 conversion to active T3, they do not affect the conversion of T4 to reverse T3. Reverse T3 is an antagonist to active T3. If reverse T3 is occupying the receptor site, active T3 cannot get into the cell to do its job. The job of active T3 is to increase metabolism and to give the body energy. The effect of reverse T3 occupying the receptor site will be a sluggish metabolism and decreased energy. The solution is to supplement selenium and reduce stress.

(6) The other halogens (chlorine, fluorine, and bromine) are all very similar chemically to iodine and compete with it in the production of T4. A T4 molecule is tyrosine (an amino acid) with four iodine molecules attached. If other halogen molecules replace the iodine molecules, an unusable T4 molecule is formed. This is a waste of energy and a waste of iodine. This can cause thyroid problems. Two solutions are:

(a) To drink only reverse osmosis or distilled water and

(b) To get a shower filter to help remove chorine and fluorine from the shower water.

Because the skin is like a sponge and very absorbent. It is especially important for swimmers to shower immediately after leaving the pool with a filtered showerhead.

(7) Some foods interfere with thyroid function and hormone conversion. They are called goitrogenic foods and among them are cruciferous or brassica family of vegetables. The brassica or cruciferous vegetables are very high in vitamins and antioxidants and are normally very good for most people. They should be avoided by patients who have a primary thyroid dysfunction (i.e. a problem with the thyroid and not the adrenals or the pituitary gland).

If a person has a primary thyroid dysfunction and eats Brassica (cruciferous) vegetables, it is important to cook them. Cooking helps to neutralize the goitrogenic affect. If a person is taking goitrogenic foods and also taking thyroid medications or supplements, he must ensure to eat them at least two hours before or after taking thyroid medication (such as synthroid, levothyroid, or natural armour) or thyroid supplements.

Here is a list of other goitrogenic foods: Bok, Choy, Collards, Watercress, Horseradish, Broccoli, Kale, Mustard Greens Kohlrabi, Brussel, Sprout, Radishes, Cabbage, Rutabagas, Cauliflower, Turnips, Soy, Almonds, Walnuts, Tapioca, Pine, Nuts, Sorghum, Millet.

L-Carnitine is an amino acid used as a supplement. If a person is taking large doses in the realm of two to four grams a day, it will suppress thyroid function as well.

(8) Another example of secondary thyroid dysfunction occurs when the liver is backed up with toxins. The liver and kidneys are necessary for proper thyroid hormone conversion. If the liver is

backed up with other toxins, hormone conversion is put on hold or slowed down. The liver has a very heavy load detoxifying the body these days because of the myriad of pesticides, herbicides, food additives, air pollutants, water pollutants, and so on. The solution is to eat organic foods, avoid processed foods, and limit exposure to chemicals.

(9) When the kidneys do not perform the very important function of ridding the body of excess acid, the body cannot maintain a balanced pH. Balanced pH is necessary for proper enzyme function, and enzymes are necessary to convert T4 to T3.

The solution is to stay away from foods that form excessive acid such as meat, sugar, alcohol, colas, and coffee. It is important to drink plenty of water and to eat a good quantity of fresh, alkalizing vegetables. Here is a list of alkalizing vegetables:

Broccoflower, Jicama, Onion, Bell, Pepper, Okra ,Parsnip, Beets, Squashes, Asparagus, Eggplant, Collard, Greens, Parsley, Celery, Endive, Turnip, Greens, Cucumber, Potato, *Cauliflower, *Brussels Sprouts, *Mustard Greens, *Broccoli, *Kale

The vegetables marked with a * are goitrogenic; remember to cook them and eat them two hours before or after taking thyroid medication or thyroid supplements.

(10) If the body is high in estrogen or estrogen mimics (for example, pesticides or herbicides), it causes production of excessive amounts of Thyroid Binding Globulin (TBG). T4 needs to be free of any adjoining proteins, such as TBG, in order to convert to active T3. TBG attaches to free T4, making it unavailable for conversion to T3. Sensing inadequate amounts of free T4 in the blood stream, the pituitary gland releases TSH (thyroid stimulating hormone), which tells the thyroid to overwork making more T4. This over stimulation can cause a goitre and if the body does not get enough T4, it can't keep up with its metabolic needs. This shuts things down metabolically and causes weight gain. Liver function is very important in getting rid of estrogen and estrogen mimics. Use liver detoxifying agents to support its functioning. Regular bowel elimination is very important for getting rid of excess estrogen. Exercise, water, and fiber are basic to regular bowel elimination. Hypothyroid patients are usually constipated and might need to supplement with Magnesium Citrate. Magnesium Citrate works to stimulate the smooth muscle of the colon, causing peristalsis. Stay away from synthetic or chemical estrogens such as the pill, Premarin, Provera, pesticides, herbicides, etc.

(11) Consumption of bad fats (trans fats or hydrogenated oils, such as those found in fried foods) will cause cell membrane to become very rigid and not allow molecules to pass through with ease. Once the T3 molecule has successfully landed on the receptor site, it must now pass through the cell's phospholipid membrane. For healthy, fluid membranes, plenty of omega 3 essential fatty acids are essential. Flax seed and salmon are excellent sources of omega 3 essential fatty acids.

(12) When extra sugar builds up in the bloodstream, it attaches to proteins (this process is called glycosilation) and impairs protein function. T3 receptors are these types of proteins; consequently, their functions are impaired when there is too much sugar in the bloodstream. It is important to keep the blood sugar balanced.

(13) Vitamin A deficiency can cause thyroid dysfunction. The T3 receptor site on the cell needs Vitamin A in order to have good bonding ability.

(14) Vitamin D deficiency can contribute to thyroid dysfunction. Vitamin D helps to suppress any autoantibodies that may be attacking own thyroid gland. Hashimoto's Disease is an autoimmune

disease that is the most common cause of this problem. Autoantibodies can be detected with a test called the comprehensive Thyroid Blood Panel.

DIAGNOSIS

Whenever a person has a goitre or thyroid nodule, three questions must be answered.

First, is the gland, or a portion of it, so large that it is stretching, compressing, or invading nearby structures? Thyroid swelling can cause a sensation of tightness or, less commonly, pain in the front of the neck. A goitre or nodule can compress the trachea causing cough or shortness of breath, while pressure on the esophagus can cause discomfort with swallowing. When a goitre extends down into the chest, blood returning from the neck and head can be partially obstructed, causing neck veins to bulge. When a goitre or nodule is due to cancer, the tumor may actually grow into nearby structures, causing pain, hoarseness or coughing up blood when the trachea is penetrated.

Second, is the gland functioning normally, or is it overactive or underactive? Goitre is a characteristic feature of all the common forms of hyperthyroidism. For example, in hyperthyroid Grave's disease, there is usually a diffuse or generalized goitre; and in toxic adenomas and toxic multinodular goitre, there are solitary and multiple nodules, respectively in the gland. Individuals with hyperthyroidism due to either painless thyroiditis or subacute thyroiditis also usually have a modest diffuse goitre. Conversely, people with hypothyroidism also often have a goitre. For example, the most common cause of hypothyroidism, autoimmune hyroiditis, typically causes diffuse gland enlargement that is 1½ to 3-times normal size. Consequently, thyroid function must be assessed in all patients presenting with goitre or a thyroid nodule. The best single test to screen for both conditions is the serum thyroid stimulating hormone (TSH) concentration, which is suppressed to a low level in people with hyperthyroidism, and elevated in those with hypothyroidism. ***Third, is the goitre or thyroid nodule due to malignancy?*** Fortunately, most patients with a goitre or thyroid nodule do not have thyroid cancer. Often other findings in a patient with a goitre, such as the features of hyperthyroid Grave's disease, make it unnecessary to do additional tests to rule out cancer. However, when a goitre is enlarging rapidly, causing local symptoms or develops in a person with risk factors for or other symptoms suggesting a malignancy, this possibility must be considered. On the other hand, almost everyone with a thyroid nodule larger than 1.0 to 1.5 cm in diameter must be investigated for the possibility of thyroid cancer.

Then, a doctor will look on physical examination for signs related to the thyroid enlargement: the entire gland or nodule size; its firmness, mobility and tenderness and whether there is any nearby lymph node enlargement. The doctor will also look for signs of thyroid hormone excess or deficiency. Although the history and physical examination sometimes provide important clues, it is almost always necessary to perform additional diagnostic tests to answer the key clinical questions with certainty.

A thyroid sonogram beams inaudible sound waves into the neck and the returning echoes depict thyroid and surrounding tissues; this can confirm that a lump in the neck is in the thyroid gland, show whether it is cystic or solid, and precisely measure its size. A blood test for TSH can rule in or out all of the common causes of hyperthyroidism and hypothyroidism. If the TSH is low, then there is a possibility the person has a benign, but hyper functioning thyroid adenoma; so the next step for these individuals is often a radionuclide thyroid scan to see if the gland enlargement is, in fact, a "hot" nodule. This is important, because almost all cancerous thyroid nodules are "cold" on radionuclide scanning; unfortunately, so are many benign thyroid nodules, so the test is not very helpful in people who do not already have a low TSH blood test suggesting hyperthyroidism. If the TSH is elevated, the person probably has an

underactive thyroid gland, and its enlargement may be a sign of autoimmune thyroiditis. If the TSH is normal or high, then most individuals with a thyroid nodule larger than 1.0 to 1.5 cm (1/2 inch) in diameter as well as those with a suspicious goitre need to have a fine needle aspiration biopsy to obtain thyroid cells for cytological evaluation by an expert pathologist. Thyroid biopsy results fall into four categories.

First is an inadequate specimen in which there simply is not enough thyroid tissue to make a diagnosis. People with this finding need another biopsy. **Second,** and fortunately, most often, the biopsy report is benign. People with this category of nodule usually need no surgery and can be seen by their doctor periodically to sure their goitre or nodule is not progressively enlarging. **Third**, the biopsy can strongly suggest the presence of thyroid cancer. When the biopsy findings are malignant, 95% of the time, the person will actually prove to have thyroid cancer at subsequent surgery, so an operation is indicated unless the individual has other serious medical problems. The **fourth** category of thyroid biopsy finding is uncertain or indeterminate. One in five biopsies fall into this group, in which adequate tissue has been obtained, but the features of the cells seen just are not characteristic enough of a benign or malignant nodule to be sure. Surgery is usually also indicated for this last group, because among people with this biopsy outcome, 15% will prove to have thyroid cancer once the nodule is removed surgically and fully examined.

MEDICAL TREATMENT

Whether a goitre needs treatment depends on the answers to the three key clinical questions. If the thyroid is so large as to cause symptoms by stretching or compressing adjacent structures or if it is so big as to be unsightly, surgical removal of the thyroid gland (thyroidectomy) may be required. If the goitre is related to a condition causing hyperthyroidism, as in Grave's disease or toxic nodular goitre, treatment with radioactive iodine may be effective in both controlling gland overactivity and decreasing its size. Some normally functioning (nontoxic) nodular goitres can also be shrunk with radioactive iodine therapy. If the thyroid is enlarged as the result of autoimmune (Hashimoto) thyroiditis and the gland is also underactive with a high blood TSH level, then starting thyroid hormone medication (L-thyroxine) may both treat the hypothyroidism and partially shrink the gland. Similarly, thyroid nodules may also require surgical removal or radioactive iodine based on their size and whether they are causing hyperthyroidism. In addition, thyroid nodules that are found to be suspicious for malignancy must be removed along with the remainder of the thyroid gland to prevent the spread of thyroid cancer. Most people with a cytologically uncertain finding are also advised to have at least the half of their thyroid gland with the nodule removed because one in seven of these individuals will be found to have thyroid cancer. The use of thyroid hormone to put the thyroid gland to rest and shrink thyroid nodules often prescribed in the past has now been found to be relatively ineffective.

Several treatment modalities are available for patients with multi nodular goitres (MNGs). The selection of the best therapeutic option will depend on several factors, including goitre size, location, the presence and severity of compressive symptoms and the presence or absence of thyrotoxicosis.

The treatment will depend upon the cause of the goitre. If the goitre was due to a deficiency of iodine in the diet, the patient is given iodine supplementation by mouth. This will lead to a reduction in the size of the goitre, but often the goitre will not completely resolve. If the goitre is due to Hashimoto's Thyroiditis and the person is hypothyroid, the patient is given thyroid hormone supplement as a daily pill. This treatment will restore thyroid hormone levels to normal, but does not usually make the goitre go completely away. While the goitre may get smaller, sometimes there is too much scar tissue in the gland to allow it to get much smaller.

However, thyroid hormone treatment will usually prevent it from getting any larger. If the goitre is due to hyperthyroidism, the treatment will depend upon the cause of the hyperthyroidism. For some causes of hyperthyroidism, the treatment may lead to a disappearance of the goitre. For example, treatment of Graves' disease with radioactive iodine usually leads to a decrease or disappearance of the goitre.

Many goitres, such as the multinodular goitre, are associated with normal levels of thyroid hormone in the blood. These goitres usually do not require any specific treatment after the appropriate diagnosis is made. If no specific treatment is suggested, the patient may be warned that he is at risk for becoming hypothyroid or hyperthyroid in the future. However, if there are problems associated with the size of the thyroid per se, such as the goitre getting so large that it constricts the airway, the doctor may suggest that the goitre be treated by surgical removal.

Radioiodine (RAI) has been widely and effectively used for the treatment of toxic multi nodular goitres [23]. Administered orally, usually as a single dose, it is rapidly concentrated in thyroid tissue and results in the destruction of toxic nodules over a period of two to four months. Some patients, particularly those with severe hyperthyroidism or large goitres, may require more than one dose to achieve euthyroidism. Radioiodine is preferentially accumulated in the hyperfunctioning nodules and, therefore, subsequent rates of hypothyroidism are much lower than in patients treated with RAI for Graves' disease. Patients with severe thyrotoxicosis, particularly the elderly and those with cardiac history, are often pre-treated with antithyroid drugs (methimazole [MMI] or propylthiouracil [PTU]). There is evidence that PTU, but not MMI, may reduce the effectiveness of subsequent RAI therapy in these patients [24]. Young and otherwise healthy patients do not need pre-treatment with antithyroid drugs. Although RAI has not traditionally been considered a treatment option for patients with non-toxic MNGs, several studies, mostly from Europe, have demonstrated that it is in fact both safe and effective [25–27]. This treatment has the advantage of resulting in significant goitre size reduction (30–60%), most of which occurs within the first year after treatment with improvement in obstructive symptoms (dyspnea, dysphagia) in most patients [28, 29] and in one study RAI was shown to be more effective than levothyroxine therapy [30] in reducing goitre size. Transient hyperthyroidism may occur in the first two weeks after RAI treatment, and permanent hypothyroidism has been reported in up to 45% of patients [30].

Pre-treatment with recombinant human TSH (rhTSH) has been evaluated in recent years as adjuvant to RAI in several studies as a means to enhance the efficacy of RAI uptake in non-toxic thyroid tissue (in one study RAI uptake doubled) [31] allowing the use of lower doses of RAI [32] and enhancing goitre size reduction [31,33–36]. Additionally, pre-treatment with rhTSH has been shown to modify the regional distribution of RAI by stimulating RAI uptake in relatively hypofunctioning regions within a goitre [37]. Painful transient thyroiditis and transient mild thyrotoxicosis [33] usually within the first month after treatment, and increased incidence of subsequent hypothyroidism have been described. Additionally, an increase in goitre size with rhTSH is a potential concern, especially in patients with very large goitres in whom obstructive symptoms could be transiently worsened shortly after treatment [38]. Development of Grave's hyperthyroidism (with high levels of TSH-receptor antibodies) has been described after treatment with RAI in patients with MNGs and seems to be more common in those with high thyroid peroxidase (TPO) antibody concentrations before the treatment [39]

SURGICAL TREATMENT

Surgery is indicated for:

1. Increase in size while on TSH suppression
2. Pressure symptoms
3. Toxic changes

4. Suspected or proven malignancy
5. Cosmetic reasons

Partial, subtotal, near-total and total thyroidectomy are all accepted and practiced procedures for endemic goitre when surgery is indicated. Post-operative thyroxine is only given when there is evidence of compensated or overt hypothyroidism three months after thyroidectomy or when the amount of residual thyroid tissue at surgery is deemed too small to avoid post-operative hypothyroidism. Annual follow-ups are used to monitor thyroid function and recurrences. Post-operative compensated hypothyroidism is an indication for thyroid replacement therapy as such goitres would inevitably recur because of the TSH overstimulation. However, if a patient remains euthyroid with a TSH level in the mid-range, thyroxine is not given. Salt iodization is adequate and closely monitored in our region.

PREVENTION

The supply of adequate iodine in the diet and the elimination of goitrogens are the means used to prevent endemic goitre. However, there is increasing evidence endemic goitre could be provoked by genetic [40] as well as environmental factors including emotional stress, smoking and infections. Global iodization of salt has been successfully introduced with remarkable results in the last 80 years after its initial successful introduction in Switzerland and the state of Michigan in the early part of the 20th century. The technology of iodination is simple, and its production is easy to regulate. This is the preferred method of prophylaxis because salt consumption is consistent and universal. Up to 1999 only 28% of the European population had access to iodized salt, making it the worst in the world. Globally 68% of the world population had access to iodized salt at that time [5]. Recent cross-sectional data on urinary iodine (UI) and total goitre prevalence (TGP) in school-age children from the WHO Global data base on iodine deficiency indicate a marked improvement in the worldwide iodine deficiency disorders (IDD) situation. Nevertheless, IDD is still a cause for concern. It is still a public health problem in 54 WHO member countries, in spite of previous optimism that it would be eliminated by the year 2000 [3].

Iodine in the form of potassium iodide is added to table salt in varying amounts ranging from 1 part in 10000 of salt to 1 part in 200000, depending on local factors such as customary consumption of salt. Potassium iodide is preferred in humans because of its increased stability. Surveys have confirmed the dramatic reduction in the prevalence of goitre and gradual disappearance of cretinism within a few years of introduction of iodized salt [41]. Difficulties in implementation occur in countries where locally inexpensive salt is available and government programs to increase iodine consumption are lacking [42]. Benede et al did a cross-sectional study and found iodine deficiency of moderate severity in a rural community in KwaZulu Natal with no iodine supplementation program, in spite of the fact that South Africa was considered officially iodine sufficient [43].

Iodination of vegetable oil is also in use in areas where salt consumption is not common either due to geographical barriers or cultural factors. It has also been helpful for initiating the start-up phase of prevention programs using iodized salt awaiting approvals or health legislation [44]. There have been concerns about the increase in cases of iodine induced hyperthyroidism (IIH) after implementation of iodization programs. This has been shown to be rare following well executed iodine supplementation programs [45]. The enormous benefits of correcting iodine deficiency far outweigh the occurrence of thyrotoxicosis in iodine deficient regions. Overall, it abolishes endemic goitre and reduces the incidence of toxic nodular goitres in the long run. At the World Summit for Children in 1990 attended by 71 heads of state, it was decided to eliminate IDD by the year 2000. This was to be accomplished by universal salt iodination by 1995. So far all the 192 WHO member states have signed the declaration [3]. Unfortunately, IDDs were not eliminated by the year 2000 as projected

but significant progress was made as per the findings of the WHO Global Database on Iodine Deficiency of 2004 in which 126 member countries participated representing 92.1% of the world's school-age children [3].

The cost of salt iodination is currently estimated at 5 US cents per person per year. There are concerted efforts and campaigns in affected countries to convince governments, salt producers and relevant organizations of the cost effectiveness of salt iodination.

PERSISTENCE OF GOITRE IN POST IODINIZATION PHASE

Persistence of endemic goitre after adequate iodization have been observed by many authors all over the world [46, 47]. This suggests that there might be other goitrogens or factors playing a role besides iodine deficiency that need to be explored. After iodine supplementation programme, thyroid autoimmunity has been considered as an important cause for persistence of goitre [46, 48]. However, a study from India found thyroid antibody positivity in only 7.3 per cent of children [49]. Several authors have assessed thyroid function status in goitrous children from both endemic and iodine supplemented regions and found the prevalence of hypothyroidism (subclinical and overt) ranging from 0-40 per cent [50, 51]. A large study in India has found that 4.3 per cent children with goitre and 2.3 per cent of normal children had subclinical hypothyroidism [52]. Iron deficiency state is an important cause for persistence of goitre in the iodine replete population [53, 54]. Hess et al have shown that supplementing iron in iron-deficient children with goitre decreases its size [55]. Selenium as a causative factor for goitre formation has been explained by diminished activity of selenocysteine enzymes in thyroid, notably glutathione peroxidase and deiodinase type-1 in selenium deficiency [56, 57]. Though the normal range of serum selenium level has not been defined, plasma selenium concentration of 70-90 µg/l is required for optimal activity of glutathione peroxidase as shown in many experimental models [58]. Low selenium level has been shown in several areas of Iran, Middle East and some European countries and it has been linked to the persistence of high goitre prevalence [58, 59].

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