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Samiran Sana
Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore, Bangladesh

Sadiur Rahman Sajon
Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore, Bangladesh

Sohel Rana
Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore, Bangladesh

Zobaida Mostarin Nishi
Department of Pharmacy, School of Medicine, University of Asia Pacific, Dhaka, Bangladesh

Niaz Mahmud
Department of Nutrition and Food Technology, Faculty of Applied Science and Technology, Jessore University of Science and Technology, Jessore, Bangladesh

Correspondence
Sadiur Rahman Sajon
Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore, Bangladesh

A short review on congenital hypothyroidism, environmental thyroiditis and current status of thyroid disease in Bangladesh

Samiran Sana, Sadiur Rahman Sajon, Sohel Rana, Zobaida Mostarin Nishi and Niaz Mahmud

Abstract
Thyroid disease is a common endocrine disorder resulting from their impaired activity at tissue level. Congenital hypothyroidism and environmental thyroiditis are two major concern now-a-days. Congenital hypothyroidism is broadly classified into Primary hypothyroidism, secondary hypothyroidism, peripheral hypothyroidism, syndromic hypothyroidism and transient congenital hypothyroidism. Factors affecting congenital hypothyroidism may include thyroid dyshormonogenesis, thyroid dysgenesis, resistance to TH binding, defects in T3 and T4 release or even genetic factor. Factors that increase environmental thyroid disease risk include radiation exposure, both from nuclear fallout and medical radiation, increased iodine intake, as well as several contaminants in the environment that influence the thyroid. In Bangladesh the overall state of thyroid disease is greatly influenced by gender and diseases like diabetes. Necessary steps should be taken to raise awareness among mass people about Hypothyroidism and enlighten them to make stand against this disease.

Keywords: congenital hypothyroidism, environmental thyroiditis, Bangladesh, hypothyroidism survey data

Introduction
Hypothyroidism is a familiar endocrine disease which is a consequent from insufficiency of thyroid hormone or, more rarely, from their retarded function of thyroid gland. The thyroid gland is a butterfly-shaped tissue in the lower neck. It makes iodine-containing hormones that play an important role in regulating growth, brain development, and the rate of chemical reactions in the body. And congenital hypothyroidism is a common thyroid disorder which occurs due to insufficiency of thyroid hormone during birth. Congenital hypothyroidism affects an estimated 1 in 2,000 to 4,000 newborns. Congenital hypothyroidism affects more than twice as many females as males [1]. It is a heterogenic disorder that may be caused by dysregulation in one or more biosynthetic pathway due to genetic regulation. Environmental agents intervene with thyroid function at multiple sites, additionally thyroid hormone synthesis, thyroid hormone metabolism and excretion, and thyroid hormone action (2–5). Unnatural thyroid function detected in combination with an environmental exposure is generally thought to be a direct effect of the factors. These facts are best interpreted with familiarity with the factors that can influence thyroid function, including thyroid autoantibody level, iodine intake, smoking history, family history of autoimmune thyroid disease, pregnancy, and medicament usage. In most studies, these details are not all available.
However, the current review has been made to highlight the congenital and environmental factors affecting the hypothyroidism and current status of Bangladesh in thyroid disorders so that it might be helpful in the future to diagnose and pinpoint the actual key factors behind the disease-hypothyroidism and other thyroid disorders in Bangladesh perspective.

Thyroid physiology
Thyroid hormones are the only iodine-containing substances of physiologic importance in vertebrates. Thyroid cells actively extract and pertain iodide from plasma. T4, a prohormone, is converted to triiodo-thyronine (T3), the efficacious form of thyroid hormone, in the peripheral tissues by 5'-deiodination. Prematurely in the disease mechanism, mandatory mechanisms maintain T3 levels. Regular thyroid hormones produces all of the circulating T4 and T3 (about 20%) [6] and most cellular activity of thyroid hormones are resultant of T3

which has greater affinity (4 to 10 times) for receptors than T4 [7, 8]. 80% of serum T3 is obtained from the deiodination of T4 in tissues such as the liver and kidney. Genetic factors also plays an important role in regulating thyroid hormone production. Figure 1 depicts the gene mediated regulation of thyroid hormonogenesis.

Once T4 and T3 are secreted into the blood flow, they are bound by thyroxine-binding globulin (TBG), transthyretin (thyroxine-binding prealbumin), and albumin. Only the free (unbound) flowing T4 and T3 is capable of binding to specific thyroid hormone receptors in peripheral tissues and possesses biologic activity. Normally, nearly 0.03% of T4 and 0.5% of T3 is free (9, 10).

Changes in the binding ability of thyroid hormone transport proteins may notably affect the calculation of total thyroid hormone concentration and thereby create complication in the diagnosis of hypothyroidism. The accurate diagnosis of thyroid disease is more difficult in patients with multiple abnormalities in thyroid hormone-binding proteins (11).

Pathophysiology [12]

Most common cause of hypothyroidism is the localized disorder of the thyroid gland that results in decreased thyroid hormone production. Under normal conditions, the thyroid releases 100 to 125 mol of T4 daily and only small amounts of T3. Reduced production of T4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and thyroid T4-5'- deiodinase action. This in turn causes the thyroid to release more T3. Deficiency of the hormone has a wide range of effects, because all metabolically active cells require thyroid hormone. Systemic effects are cause of either derangements in metabolic processes or direct effects by myxedematous infiltration (that is, aggregation of glucosaminoglycans in the tissues).

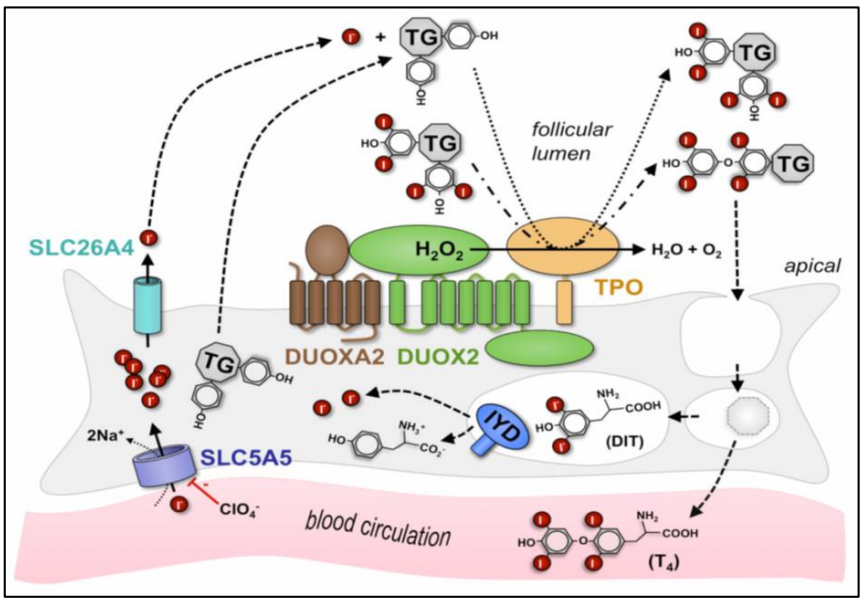

Fig 1: Schematic drawing of a follicular thyroid cell illustrating the key players involved in thyroid hormonogenesis.

The distinct steps comprise 1) the active uptake of iodide from the blood circulation via the sodium-iodide symporter (SLC5A5); 2) the facilitated efflux of iodide into the colloid via an apical anion channel (SLC26A4); 3) iodination of tyrosine groups of thyroglobulin (TG) catalyzed by thyroid peroxidase (TPO); 4) subsequent coupling of iodinated tyrosines within TG via ether-bond formation to iodothyronines; steps 3 and 4 require hydrogen peroxide as co-substrate, which is provided by a hydrogen peroxide generating NADPH-oxidase constituted by dual oxidase 2 (DUOX2) and its maturation factor (DUOXA2); 5) following endocytosis, iodothyronines (T4>T3) are liberated by lysosomal degradation of the TG matrix protein; 6) concomitantly released iodotyrosines are dehalogenated by iodotyrosine deiodinase (IYD) allowing 'recycling' of iodide for further hormone synthesis [13].

Congenital Hypothyroidism

Congenital Hypothyroidism (CH) is the name for babies born with hypothyroidism due to the thyroid gland being absent or severely deficient. If it is not detected and treated early irreversible neurological problems and poor growth can occur. 75% of cases of CH may be due to a total or incomplete development of the thyroid, which is not inherited or a failure of pituitary control (TSH is absent). 10% of cases are due to an enzymic failure in the manufacture of thyroid hormones, (defects in thyroglobulin), which is usually inherited so there may be a risk to further infants. 5% of cases are due to hypothalamic-pituitary dysfunction and this type of dysfunction usually causes other disorders such as lack of growth hormone etc. This type of cause may include tumours, arterial blockage and congential defects. 5% of patients will also have other congenital defects and in some cases there are genetic defects that have caused CH. Lack of early treatment may cause delayed mental development, learning difficulties and poor co-ordination. Some cases are due to other causes such as the mother taking medications or having thyroid antibodies that have crossed the placenta. This kind of problem improves after delivery of the baby [14].

Symptoms [15]

Over half the babies born with CHT look entirely normal and have no obvious symptoms at all. That is why it is so important that all children are tested at birth. CHT can often be diagnosed before the baby shows any definite signs of the condition. Some babies with hypothyroidism are sleepy and

difficult to feed, although lots of babies have these symptoms without being hypothyroid! This really highlights the importance of screening for CHT in all newborn babies. Other symptoms may include constipation, low muscle tone (floppiness), cold extremities, and poor growth. Some hypothyroid babies have prolonged jaundice (with an associated yellow skin) after birth. Although some children with CHT have development problems, the likelihood of a significant long-lasting effect is low as long as appropriate treatment is started promptly. If your child is diagnosed with CHT the doctor will examine them very carefully to check for any other problems.

Signs

The physical findings of hypothyroidism may or may not be present at birth. Signs include the following: coarse facial features, macroglossia, large fontanelles, umbilical hernia, mottled, cool, and dry skin, developmental delay, pallor, myxedema, Goiter etc. [16]. The typical appearance of a hypothyroid infant before the advent of newborn screening is shown in the infant in Figure 2 [17]. Features include jaundice, a puffy face and wide posterior fontanelle with open sutures. The nasal bridge is flat and the eyes exhibit pseudo hypertelorism. The mouth may be slightly open revealing macroglossia. Further examination would reveal a protuberant abdomen with a large umbilical hernia. Skin may be cool to touch and mottled in appearance reflecting circulatory compromise [18]. Gene mutations causing congenital hypothyroidism can be a rare cause of distinct clinical phenotypes. Most well-known is Pendred's syndrome. Affected patients have sensorineural deafness, hypothyroidism and goiter. This syndrome is due to a defect in pendrin, which is a transmembrane chloride-iodide transporter expressed in both the thyroid gland and the inner ear [19]. A mutation in thyroid transcription factor 2 (TTF-2) causes a syndrome of thyroid dysgenesis, choanal atresia, cleft palate and spiky hair also known as Bamforth-Lazarus syndrome [20] (Figure 3).

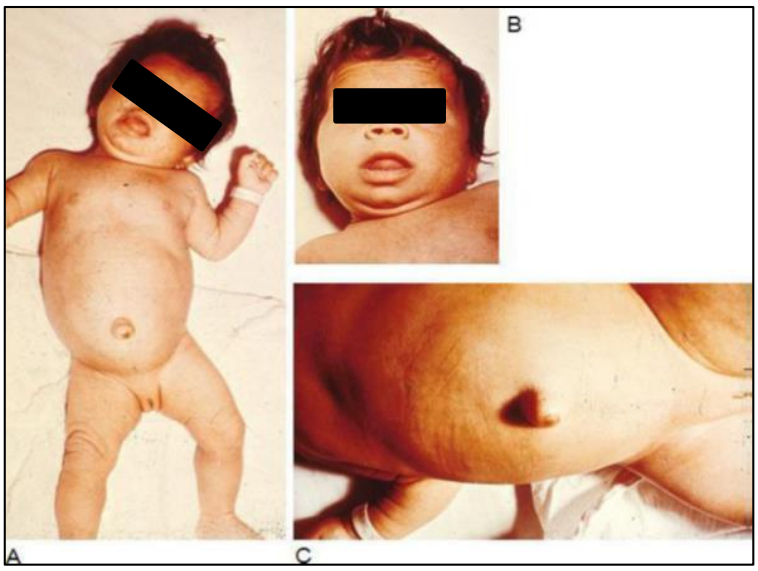

Fig 2: Infant with congenital hypothyroidism. A - 3 month old infant with untreated CH; picture demonstrates hypotonic posture, myxedematous facies, macroglossia, and umbilical hernia. B - Same infant, close up of face, showing myxedematous facies, macroglossia, and skin mottling. C - Same infant, close up showing abdominal distension and umbilical hernia [17].

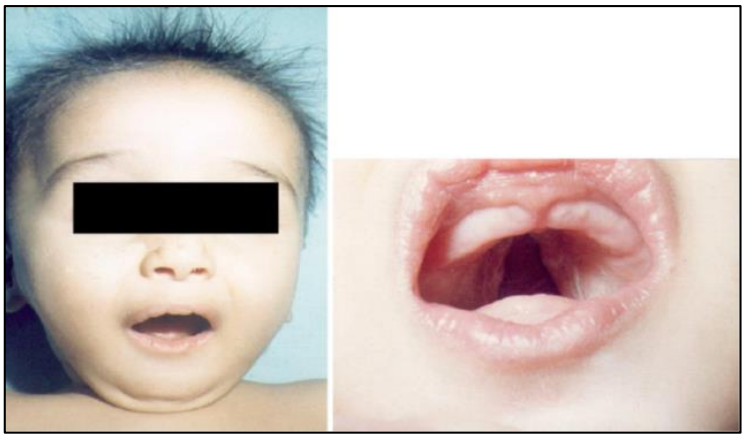

Fig 3: Figure 2: Bamforth- Lazarus syndrome. An 8 month old infant with a homozygous mutation in the TTF-2 gene locus leading to congenital hypothyroidism. Phenotypic features include, low set ears, extensive cleft palate, hypertelorism, spiky hair and low posterior hairline. (Taken from; A novel loss-of-function mutation in TTF-2 is associated with congenital hypothyroidism, thyroid agenesis and cleft palate; Human Molecular Genetics, 2002, Vol. 11, No. 17. Courtesy Dr. Michel Polak and the Oxford University Press.) [17]

Etiology

Permanent congenital hypothyroidism may be due to primary or secondary (central) causes. Primary causes include defects of thyroid gland development, deficiencies in thyroid

hormone production, and hypothyroidism resulting from defects of TSH binding or signal transduction. Peripheral hypothyroidism results from defects in thyroid hormone transport, metabolism, or resistance to thyroid hormone action. Secondary or central causes include defects of thyrotropin releasing hormone (TRH) formation or binding and TSH production. These are covered briefly in this review and are listed in Table 1.

Table 1: Classification and etiology of congenital hypothyroidism [18]

1. Primary hypothyroidism
Thyroid dysgenesis: hypothyroidism due to a developmental anomaly
(Thyroid ectopia, athyreosis, hypoplasia, hemiagenesis)
Associated mutations: (these account for only 2% of thyroid dysgenesis cases; 98% unknown)
TTF-2,
NKX2.1,
NKX2.5
PAX-9
Thyroid dyshormonogenesis: hypothyroidism due to impaired hormone production
Associated mutations:
Sodium-iodide symporter defect
Thyroid peroxidase defects
Hydrogen peroxide generation defects (DUOX2, DUOXA2 gene mutations)
Pendrin defect (Pendred syndrome)
Thyroglobulin defect
Iodotyrosine deiodinase defect (DEHAL1, SECISBP2 gene mutations)
Resistance to TSH binding or signaling
Associated mutations:
TSH receptor defect
G-protein mutation: pseudohypoparathyroidism type 1a
2. Central hypothyroidism (secondary hypothyroidism)
Isolated TSH deficiency (TSH b subunit gene mutation)
Thyrotropin-releasing hormone deficiency
Isolated, pituitary stalk interruption syndrome (PSIS), hypothalamic lesion, e.g. hamartoma
Thyrotropin-releasing hormone resistance
TRH receptor gene mutation
Hypothyroidism due to deficient transcription factors involved in pituitary development or function HESX1, LHX3, LHX4, PIT1, PROP1 gene mutations
3. Peripheral hypothyroidism
Resistance to thyroid hormone
Thyroid receptor b mutation
Abnormalities of thyroid hormone transport
Allan-Herndon-Dudley syndrome (monocarboxylase transporter 8 [MCT8] gene mutation)
4. Syndromic Hypothyroidism
Pendred syndrome - (hypothyroidism- deafness - goiter) Pendrin mutation
Bamforth-Lazarus syndrome - (hypothyroidism - cleft palate - spiky hair) TTF-2 mutation
Ectodermal dysplasia - (hypohidrotic - hypothyroidism - ciliary dyskinesia)
Hypothyroidism - (dysmorphism - postaxial polydactyly - intellectual deficit)
Kocher - Deber - Semilange syndrome - (muscular pseudohypertrophy- hypothyroidism)
Benign chorea - hypothyroidism
Choreoathetosis - (hypothyroidism - neonatal respiratory distress) NKX2.1 /TTF-1 mutation
Obesity - colitis - (hypothyroidism - cardiac hypertrophy - developmental delay)
5. Transient Congenital Hypothyroidism
Maternal intake of antithyroid drugs
Transplacental passage of maternal TSH receptor blocking antibodies
Maternal and neonatal iodine deficiency or excess
Heterozygous mutations of THOX2 or DUOXA2
Congenital hepatic hemangioma/hemangioendothelioma

Transient hypothyroidism may be caused by maternal or neonatal factors. Maternal factors include antithyroid medications, transplacental thyrotropin receptor blocking antibodies and exposure to iodine deficiency or excess. Neonatal factors include, neonatal iodine deficiency or excess, congenital liver hemangiomas and mutations in the genes encoding for DUOX and DUOXA2 (see Table 2).

Environmental factors in Hypothyroidism

The common model of the onset of autoimmune thyroid disease involves an underlying genetic predisposition and a trigger (s) that initiate the cascade of events and sustain the process, culminating in thyroid hypofunction or hyperfunction. This process has been extensively studied and described [21]. It has been estimated, based on twin studies [22], that 70%–80% of susceptibility to autoimmune thyroid disease is on a genetic basis. The remaining 20%–30% contribution to the onset of autoimmune thyroid disease is thought to be due to environmental exposures or triggers. There are a number of exposures that have been identified and proposed, both from human and animal studies [23-26]. These include infections, life stress, iodine intake, smoking,

medications such as amiodarone and interferon, radiation, and environmental toxicants. The environmental factors most closely associated with susceptibility to autoimmune thyroid disease include radiation, iodine intake, and environmental toxicants. The mechanism of action for most thyroid toxicants is not established, but this information is not required to make an association of exposure with thyroid dysfunction. Although there are limited data in this area to translate to the management of individual patients, there are findings that can contribute to a strategy of risk reduction.

Radiation

Radiation is perhaps the best characterized environmental exposure linked to effects on the thyroid. The most common thyroid manifestation of radiation is hypofunction, as well as thyroid nodules and thyroid cancer. Autoimmune thyroid disease has been linked to therapeutic medical radiation [27-29], as well as environmental radiation exposure [30-35]. Both the atomic bomb detonations in Japan [31] and nuclear contamination from the Chernobyl nuclear power plant accident [34] have been associated with an increased risk of autoimmune thyroid disease. This association, however, has not been a consistent finding in all studies, with several showing no effect [31, 35]. Several studies showed thyroid dysregulation in the human body due to radiation exposure [36, 37]. The thyroid manifestations of radiation exposure vary, likely due to underlying genetic susceptibility, iodine intake, and pattern of radiation exposure. Some individuals have thyroid destruction, others develop nodules and cancer, and others activate thyroid autoantibodies, some of whom, in a specific time frame, develop autoimmune thyroid disease.

Environmental chemicals

A wide range of environmental toxicants have been identified that interfere with thyroid hormone production, metabolism and action. Most of these agents, at sufficient doses, interfere with thyroid function and their effect can be detected by an elevation in serum TSH or a reduction in serum thyroxine (T4) or T3 [38]. There are also some agents, such as polychlorinated biphenyls (PCBs) that may have intrinsic thyroid hormone agonist actions [38]. The challenge with any toxicant is to link exposure in an individual to specific actions on thyroid function.

The ways in which environmental toxicants and chemicals affect thyroid function include; [39, 40].

1. Alteration of thyroid hormone metabolism
2. Direct toxic effect on the gland changing function and regulation
3. Production of thyroid antibodies (leading to autoimmune thyroid disorders)
4. Interaction with thyroid carrier proteins
5. Block iodine uptake by the thyroid gland

Polychlorinated biphenols (PCBs) and Dioxins. PCB's were once used in electrical transformers, capacitators, plasticizers and adhesives. Although many are no longer used in the U.S. they still persist in the environment. Eating fish from contaminated waters, and farm-raised fish, are a major source of PCB's as well as dairy and meat products. Dioxin a primary toxic component of agent orange, is formed as a byproduct of industrial processes involving chlorine such as waste incineration, chemical and pesticide manufacturing and paper bleaching. The main way we are currently exposed to dioxin is through our food. It is a contaminant in meat, dairy and fish. PCB's and Dioxins induce thyroid hormone metabolism through an enzyme called UDP-glucuronyl transferase. This simply means they alter liver function of the enzyme that metabolizes thyroid hormone. They also directly attack the thyroid gland and thyroid hormone carrier proteins [41]. There are numerous studies linking PCBs and Dioxins to thyroid dysfunction [42, 43].

Pesticides have also been linked to thyroid disease in numerous studies. We are exposed to pesticides everyday whether we chose to be or not. There are numerous studies that link pesticides to thyroid dysfunction. Specifically Maneb and Mancozeb which are sprayed on fruits such as bananas and has been found to alter thyroid stimulating hormone (TSH), inhibit thyroid peroxidase enzyme, and cause thyroid nodules [44].

Pentachlorophenol (PCP) is a toxic byproducts is linked to alteration of thyroid hormones and the formation of a goiter [45]. Bisphenol-A (BPA) is another common chemical that is linked to thyroid disorders [46]. Perfluoro octanoic Acid (PFOA) is found in stain and water resistant coatings for carpet, furniture, fast-food containers, paints, and foams. These chemicals build up in our adipose tissue, or fat, and alter thyroid function [47].

Heavy metals are found to affect the thyroid as well. One of the main heavy metals studied is cadmium. Cadmium is a component of cigarette smoke and a product of industry. It is in the air, soil and water of most cities. We are exposed through cigarette smoke, food grown in contaminated soil, air pollution and water contamination. There are numerous studies linking thyroid disease to cadmium exposure. Mercury is also linked to thyroid disease in women and children, which depletes selenium & it is a mineral that is essential for proper thyroid function [48]. Lead is another heavy metal that we are exposed to on a daily basis through our food, air and water. It too is linked to thyroid disorders in many studies.

One of the note shows how sensitive a woman's hormonal system is compared to men. Women's hormones appear to be more interconnected than men's hormones. For example many women develop thyroid disease during pregnancy due to increases in estrogen and progesterone. One study compared men and women's blood levels of lead and mercury to alterations in thyroid hormones and found women were more affected by the heavy metals [49]. On the other hand deficiency of the heavy metal Se was found to be a major cause of hypothyroidism specially silent hypothyroditis [50].

A recent study suggested that there may be a significant association between vitamin D deficiency and hypothyroidism [51] which is in harmony with the previous studies that showed the prevalence of vitamin D insufficiency in Hashimoto's cases (92%) was significantly higher than that observed in healthy controls (63%, $p < 0.0001$) [52, 53]. Another study shows vitamin C deficiency is in close connection with hypothyroidism.

Current Status of Bangladesh regarding Thyroid related disease

Clinical experience and few laboratory tests were the only means for evaluating thyroid disorders in Bangladesh even in the early eighties of the last century. Modern laboratory tests evolved gradually over the last 25 years making available the thyroid function tests with high sensitivity and specificity [54]. The absolute and relative number of different thyroid disorders have changed over time as iodine deficiency disorders started to decline since early nineties of the last

century. There was paucity of published reports on the spectrum of thyroid disorders in Bangladesh. The range of thyroid disorders other than iodine deficiencies was considered same in Bangladesh as in other countries of Asia [55]. However the relative prevalence of the different thyroid disorders was dominated by iodine deficiency disorders. Such a study published in 1995 where the author was a member reported 35% cases of all thyroid disorders to be due to iodine deficiency as the primary etiology. The rest were autoimmune (26%), malignant (2.58%) and other thyroid disorders [56].

There has not been enough studies done throughout Bangladesh to get a statistical view of prevalent area with thyroid disease or gender or specific disease associated with thyroid disorders. But some studies are remarkably done and some significant data were achieved through these studies.

A study conducted in Khulna district which is one of the six districts in Bangladesh situated in the southern part of the country showed that overall occurrence of thyroid disease was estimated to be 20.43%. The spectrum of thyroid disorders showed highest incidence of diffuse goitre (7.35 %), followed by sub-clinical hypothyroidism (6.59%), hypothyroidism (4.97%), hyperthyroidism (0.86%) and sub-clinical hyperthyroidism (0.65 %). The incidence of thyroid disorders was observed to be highest in the 11-45 years age group (79.89%). Female outnumbered male, the ratio being 2.5: 1 with preponderance of female subjects in all disease groups. The prevalence of all goitre was 10.49%. Of the total sub-clinical and overt hypothyroidism, the incidence of autoimmune thyroid disease was 29.29% and nongoitrous thyroid dysfunction was more common than goitrous one [57].

Another study conducted in Khulna district by Rasul *et al.* showed that Male to female baby ratio was 1.2:1. Regarding the birth weight 33.4% babies were low birth weight. TSH above 10 was found in 35 babies among whom one baby was hypothyroid and the other member of the twin was also hypothyroid although the TSH level was below 10. None of newborn had TSH level above 20. Thus frequency of congenital hypothyroidism was 1.5 per thousand living newborn [58].

Alam *et al.* conducted a study among the diabetic and non-diabetic thyroid patients and found that Out of 140 diabetic subjects studied, 70% had euthyroidism (normal), 18.6% had hypothyroidism, and 11.4% had hyperthyroidism. Serum T3, T4 and FT3 levels were low, TSH and FT4 levels were high in diabetic subjects whereas, in non-diabetic subjects all these levels were normal. In this study, 30% diabetic patients were found to abnormal thyroid hormone levels. The prevalence of thyroid disorder was higher in women (17.1%) than in men (12.9%), while hyperthyroidism were higher in males (13.3%) than in females (10%) and hypothyroidism was higher in females (20%) than in males (16.7%) [59]. Another study conducted among diabetic patients in BIRDEM hospital by Islam *et al*. showed similar outcome [60].

Another study conducted by Alam *et al*. depicted that sub-clinical thyroid dysfunction prevails in females with 12.17% occurrence whereas 6.52% in males. Furthermore, the evaluation and subsequent presence of sub-clinical conditions predicts future progression to overt disease [61].

In 2008 a study conducted showed that prevalence of subclinical hyperthyroidism and hypothyroidism was 6.5% and 15%, and prevalence of hyperprolactinemia was 43% and 21% in primary and secondary infertility respectively. Prevalence of hyperprolactinemia was higher in primary infertility and prevalence of sub-clinical hypothyroidism was higher in secondary infertility, showing no correlation between TSH and prolactin levels in these two groups [62].

In 1981-82, the Government of Bangladesh and WHO jointly conducted a survey on the status of iodine deficiency disorders of the country. It was reported that more than 30 million people in the country have the benign or primary state of goiter and other form of iodine deficiency maladies. About 11 percent of the population is affected by visible goiter, the prevalence being much higher in females. About 30 percent of the population of greater Rangpur and Dinajpur districts in the north show incidences of goiter. The incidence in Chittagong, Khulna and Mymensingh areas is also fairly high [63].

Conclusion

This review indicated the factors associated with congenital hypothyroidism, environmental thyroiditis and current condition of thyroid disorder in Bangladesh which covers the prevalent reasons for being affected by this disease. The awareness of patients is affected by their educational level and family history of the disease. Another obvious reason is that patients are conscious about their treatment but still they do not have any clear perception about their disease. From this study the need for strategic plan to increase the awareness of patients about hypothyroidism is recommended. We think, for having better understanding on hypothyroidism in our country this study should be done on a handsome number of patients not only in the big cities but also in other districts and rural regions in Bangladesh. In those study we can include the not only the hypothyroid patients but also general people both in urban and rural areas that will help people to become conscious about this disease.

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