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HYPOTHYROIDISM- UNVEILING THE FACTS REVIEW ARTICLE

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ABSTRACT

Hypothyroidism is a disease in which the thyroid gland does not produce enough thyroid hormone. It is the second most common endocrine disorder among women. Common causes are autoimmune disease such as Hashimoto‘s thyroiditis, surgical removal of the thyroid and radiation therapy. Iodine deficiency remains the commonest cause of Hypothyroidism in worldwide. There are some indications that Hypothyroidism could arise from viral infection, lifestyle disorders, environmental factors or even diet related issues like food preservatives. One of these factors disturb the mechanism of thyroid gland function and results in altered secretions of thyroid hormones. The epidemiology and causes of hypothyroidism have been briefly reviewed highlighting future directions for research.

KEYWORDS: Hypothyroidism, Iodine deficiency, Hashimoto‘s thyroiditis.

INTRODUCTION

Hypothyroidism, the clinical condition of thyroid hormone deficiency, is a common disorder in the general population. Increasing prevalence of Hypothyroidism makes it a public health challenge in our society. The impact of Hypothyroidism in reproductive age group is signifcant and it demands a viable solution to ensure the health of progeny.[1]

Hypothyroidism affects up to 5% of the general population, with a further estimated 5% being undiagnosed. Over 99% of affected patients suffer from primary hypothyroidism. Worldwide, environmental iodine deficiency is the most common cause of all thyroid disorders, including hypothyroidism, but in areas of iodine sufficiency, Hashimoto‘s disease

(Chronic autoimmune thyroiditis) is the most common cause of thyroid failure. [2]

Here, we review the background of hypothyroidism, including aetiology and epidemiology with a focus on the cause of its prevalence, especially in children and women.

Methods

A search of the literature was conducted using PubMed and general search terms such as primary hypothyroidism, epidemiology, aetiology, hypothyroid in pregnancy, Congenital hypothyroidism, its prevalence in India in particular were reviewed. Potential articles of interest were identified by title and abstract, and citation lists of articles of interest were used to identify additional literature. This article is based on previously conducted studies and does not contain any studies with animals performed by any of the authors.

Aetiology

Hypothyroidism can be classified as primary (due to thyroid hormone deficiency), secondary (due to TSH deficiency), tertiary (due to thyrotropin-releasing hormone deficiency), and peripheral (extra-thyroidal; panel). Central hypothyroidism (including both secondary and tertiary) and peripheral hypothyroidism are rare and account for less than 1% of cases.[3]

In over 99% of cases, hypothyroidism is caused by a failure of the thyroid gland to produce thyroid hormones (primary hypothyroidism). The remaining 5% of patients have hypothyroidism from other causes, including secondary hypothyroidism, caused by underproduction of TSH by the pituitary gland, tertiary hypothyroidism, caused by deficiency of thyrotropin-releasing hormone, and peripheral (extra-thyroidal) hypothyroidism. [2]

- **Impact of iodine**

Iodine is a nutrient essential for thyroid hormone (TH) synthesis. The consequences of iodine deficiency are well documented, and the global strategy to correct iodine deficiency through universal salt iodization (USI) has remarkably improved the health of populations worldwide. Yet, the relationship between iodine intake and thyroid disorders is U-shaped and both inadequate and excessive iodine intakes may provoke thyroid dysfunction.[4]

In populations that shift from severe to mild iodine deficiency, the prevalence of hypothyroidism decreases; in populations shifting from mild deficiency to optimum or excessive intake of iodine, the prevalence of autoimmune hypothyroidism increases.[3]

Worldwide, environmental iodine deficiency is the most common cause of thyroid disorders, including hypothyroidism. Iodine is an essential component of thyroid hormones, but is also thought to make the thyroid gland more antigenic. Despite the implementation of iodine supplementation programmes (e.g. salt iodization), iodine intake remains suboptimal in large parts of Europe, Africa and Asia. Socioeconomic factors may play a role in the lack of adherence to iodine supplementation programmes. [2]

In india

The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4·6% in the USA. This is possibly linked to long-standing iodine deficiency in the country, which has only been partly corrected over the past 20 years. 42 million people in India have thyroid disorders and hypothyroidism is the most common of thyroid disorders in India, affecting one in ten adults. Some of the most common symptoms are weight gain or inability to lose in spite of exercise, feeling cold, fatigue, dry skin, puffy face, among others. The prevalence of thyroid dysfunction depends on gender, age, ethnic and geographical background and most importantly on iodine intake. Therefore, data of thyroid disorders from one population cannot be extrapolated to other.[5]

Among adult people in India, the prevalence of hypothyroidism has been recently studied. In this population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%.[6]

In a study conducted to explore the prevalence of hypothyroidism in one of the northern districts of Kerala which is a coastal area, 9.6% of the population was found to be affected with hypothyroidism. Most of the participants were diagnosed for the first time during the study-related screening. It suggests the iceberg phenomenon associated with hypothyroidism is existing in the society. Participants who are on medication for hypothyroidism (21%) also showed higher TSH values. It reflects the need for accurate and updated treatment modalities for hypothyroidism.[6]

Although an easy-to-detect and inexpensive-to-treat disease, patients with hypothyroidism in India often remain undetected and untreated, and thus the disease impairs the work performance and economic productivity of Indian people‖, says Swapan Jana, a public health expert and secretary of Society for Social Pharmacology (Kolkata, India). In the past, iodine

deficiency was blamed for the occurrence of hypothyroidism in India, but the disease is still prevalent in this country, despite the promotion of iodised salt since 1983‖.[5]

Production of iodised salt in India has increased by almost nine times in the past two decades—from 0·7 million metric tons per year in 1985–86 to about 6·2 million nowadays. Despite an increase in iodised salt consumption (national coverage was 51% in 2005–06 and 71% in 2009), a 2013 study showed that 42·2% of households consumed inadequately iodised salt and 10·5% consumed salt with no iodine. –Even now, there are two major factors— poverty and inability of consumers to assess the quality of salt they purchase—that hinder iodised salt consumption in India, thereby putting a large number of people at risk of iodine deficiency.[5]

Since India adopted the universal salt iodinization programme in 1983, a decline in goitre prevalence has been observed in several parts of the country, which were previously endemic. Subclinical hypothyroidism is the most common thyroid disorder in adults and is more common in women and elderly people than in men and young people, and its incidence increases with an increase in iodine intake. Due to the asymptomatic nature of subclinical hypothyroidism, the American Thyroid Association has recommended routine thyroid-stimulating hormone (TSH) screening for both sexes at the age of 35 years and every 5 years thereafter.[7] There is often a delay in the diagnosis of this disease in the country and the main reason behind this delay is the lack of awareness and also lack of facilities, screening program and tests for this illness.[8,9]

- **Autoimmunity and Hypothyroidism**

Hypothyroidism is more common in patients with autoimmune diseases, such as type 1 diabetes, autoimmune gastric atrophy, and coeliac disease, and can occur as part of multiple autoimmune endocrinopathies. Individuals with Downs‘ syndrome or Turners‘ syndrome have an increased risk of hypothyroidism. By contrast, tobacco smoking and moderate alcohol intake are associated with a reduced risk of hypothyroidism.[3]

In iodine-sufficient areas, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (also known as Hashimoto‘s disease). High concentrations of anti-thyroid antibodies (predominantly thyroid peroxidase antibodies and anti-thyroglobulin antibodies) are present in most patients with autoimmune thyroiditis. Raised concentrations of thyroid peroxidase antibodies are also detected in about 11% of the general population.[3]

Smokers have lower thyroid peroxidase antibody concentrations than non-smokers, and incidence of autoimmune thyroiditis increases after smoking cessation. (Lancet)Furthermore, TSH levels are lower in current smokers than in former smokers, and lower in former smokers than in never smokers. Smoking initiation results in a significant decrease in serum TSH levels after 1 year in men.[10,11] Children born small for gestational age have higher serum TSH levels than children born appropriate for gestational age and are consequently more often diagnosed with subclinical hypothyroidism.[12] Other environmental factors implicated in autoimmune thyroiditis are vitamin D and selenium deficiency, and moderate alcohol intake.[11]

- **Drugs and Hypothyroidism**

Iodine-containing drugs (eg, amiodarone) can restrict thyroid hormone production through iodine overload, immediately blocking thyroid hormone synthesis (ie, Wolff-Chaikoff effect). About 14% of patients treated with amiodarone develop hypothyroidism. Lithium also causes hypothyroidism via effects on thyroid hormone synthesis and release.[3]

Hypothyroidism may occur following administration of a range of medications through various processes that interfere with endogenous thyroid function. For example, 20% of patients treated with lithium will develop hypothyroidism. Lithium increases intrathyroidal iodine content, diminishes coupling of iodotyrosine residues to T_4 and T_3, and inhibits thyroid hormone release. Hypothyroidism occurs in 5–15% of individuals receiving amiodarone. Clinically relevant thyroid dysfunction occurs in 58% and 32% of patients treated with IFNα and IL-2, respectively, in part due to activation of autoimmune processes. Hypothyroidism occurs in 18–52% of patients receiving tyrosine kinase inhibitor therapy.[13]

Hypothyroidism is common after radioiodine treatment, after hemithyroidectomy, and after neck radiation or surgery for cancer therapy. In the long term, about 80% of patients with Grave‘s disease who are treated with radioiodine will develop hypothyroidism, even when low doses are used. Hypothyroidism is reported to occur in 55% of patients treated for toxic nodular goitre[40] and about 8% of patients treated for solitary toxic nodules.[3]

- **Pregnancy and Hypothyroidism**

Pregnancy has a significant effect on the thyroid gland and its functioning. Hypothyroidismin pregnancy is defined as an increased TSH level in serum. Worldwide, several studies have reported 1.5%–4% prevalence of hypothyroidism in pregnant women. Among them, 0.3% to

0.5% had overt hypothyroidism (OH), and the rest had subclinical hypothyroidism (SCH). In India, reports on the prevalence of maternal hypothyroidism ranged between 1.2% and 67.0% in various studies.[14]

Globally, the leading cause of hypothyroidism in pregnancy is iodine deficiency, and in iodine sufficient ares most common cause is autoimmune thyroiditis. Other common causes are radio-iodine therapy, thyroidectomy, congenital hypothyroidism, drug use (i.e., rifampicin and phenytoin) and any hypothalamic-pituitary disease. Maternal thyroid hormone levels are critical to the fetus, especially in the first trimester due to inability to produce iodothyronines before ten weeks of gestation. This is the period when neurodevelopment of fetus can potentially be hampered due to deficiency of iodothyronines.[14]

In pregnancy, TPOAb positivity is seen in 2–17% of women and may accompany higher serum TSH levels during the first trimester. In more than 40% of pregnant women with thyroid autoimmunity, serum fT_4 concentration falls in the hypothyroid range during late pregnancy, which may complicate diagnosing overt hypothyroidism during the third trimester. This is due to inadequate maternal thyroid capacity in response to increased demands in thyroid hormone production imposed by stimulation of the thyroid by human chorionic gonadotropin, increases in TBG, and changes in placental deiodination and renal clearance of iodine during pregnancy. The rates of miscarriages and preterm delivery are increased in pregnant women with thyroid autoimmunity. A negative association of TPOAb positivity during pregnancy with neurodevelopment of offspring has been suggested but needs to be further investigated.[15]

Prevalence reported in the study is remarkably higher as compared to the reported prevalence of antenatal hypothyroidism in other countries. The higher burden in the Indian context may be attributed to the iodine deficiency, prevalent in many regions of the country. In this review, we found prevalence of hypothyroidism was lower among coastal areas as compared to studies conducted in non-coastal areas, though difference was nonsignificant. (p=0.059). [14]

Primary maternal hypothyroidism is characterized by an increase in the serum TSH levels during pregnancy. It is further classified as subclinical hypothyroidism (SCH) which has normal free T4 levels and overt hypothyroidism (OH) which has decreased free T4 levels. Maternal complications reported to be associated with overt hypothyroidism include pre-

eclampsia, placental abruption, polyhydramnios, oligohydramnios, hyperemesis, gestational diabetes, premature rupture of membranes, and chronic hypertension. [14]

Some epidemiological studies have also pointed towards the association of maternal hypothyroidism and adverse neurological outcomes in the progeny ranging from neurological cretinism, congenital hypothyroidism, to decreased intelligence quotient. Jansen et al. observed 1981 mother child pairs. They found that both abnormal (low or high) maternal TSH values, early in pregnancy, were associated with a smaller offspring‘s total grey matter and cortical volume as assessed by MRI. [14]

Pregnancy is a state of increased thyroid hormone requirement. i.e. majority (50–85%) of previously hypothyroid women (on treatment) need to increase their dose of thyroid supplements post conception. Pregnancy serves as a stress test for the thyroid gland, which leads to hypothyroidism in iodine deficient women or in those having limited thyroid reserve. Furthermore, risk factors such as geographical disparity (in terms of iodine-deficient regions especially across India), obesity, prior history of thyroid dysfunction, the genetic history of thyroid dysfunction, and history of autoimmune disorders also make pregnant women more susceptible to hypothyroidism.[6]

Current status in India: Recent Indian studies report both higher occurrence of thyroid gland dysfunction in adults and a parallel increase in prevalence of congenital hypothyroidism (CH) in newborns. Dyshormonogenetic goiters believed to be due to genetically determined iodine handling disorders cause various enzymes defects, impaired biosynthesis of thyroid hormones and result in congenital hypothyroidism.[9]

Congenital hypothyroidism

Among the various varieties of hypothyroidism, congenital hypothyroidism is probably the most important and the commonest metabolic disorder in newborn. It is one of the most common preventable and treatable cause of intellectual impairment in children. Studies from Mumbai have suggested that congenital hypothyroidism is common in India, the disease occurring in 1 out of 2640 neonates, when compared with the worldwide average value of 1 in 3800 subjects. CH is the major cause for preventable mental retardation in infants. Usual causes of primary CH are commonly grouped together as thyroid dysgenesis which includes

maldevelopment (aplasia, hypoplasia) and maldescent (ectopia); also dyshormonogenesis and thyroiditis.[6,8]

Among known etiologies, dysgenesis due to abnormal anatomical development and dyshormonogenesis as a result of deranged physiological functioning of fetal thyroid gland account for at least 90 % of causes of CH. While review of literature report thyroid dysgenesis as the most common etiology of CH currently focus is on iodine status adequacy in women before and during pregnancy and after delivery and lactation. Worldwide reports of previously iodine sufficient countries declared presently as iodine insufficient and recent publications of several Indian states consuming lesser amounts of iodized salt seem to indicate that iodine related pathophysiological factors are emerging as predominant etiologies of CH. The most vulnerable pregnant women and newborns are prone to be affected with iodine imbalances leading to pregnancy and perinatal related complications. Analysis of demographic, biochemical, clinical and statistical data by Indian Council of Medical Research (ICMR) in a multi-centric pilot study on congenital hypothyroidism has clearly shown that dyshormonogenesis is a leading cause of CH in neonates born in India.[9]

While Western literature report dysgenesis as most common etiology of CH, dyshormonogenesis (DH) seems commoner in Indian population. As per recent global estimate, 1.88 billion people are at risk of iodine deficiency. 241 million children have an inadequate iodine intake and over half the children with insufficient iodine intake live in South-East Asia and Africa. Among Indian populations based studies, there is a gradual rise in number of children with thyroid dyshormonogenesis compared to thyroid dysgenesis. Major regional risk factors attributed and observed in ICMR pilot study at Chennai centre are consanguineous marriages, practice of marriages among natives of the same district and caste groups particularly in South India. Currently Iodine Handling Disorders with iodine imbalances appear to be major factors in etiopathogenesis of CH. It has been reported that in iodine deficient neonates turnover rate of intra thyroidal iodine is markedly accelerated and thyroid failure is more likely to occur. Thus a combined etiological role for both genetic and environmental factors seem to contribute for the occurrence of dyshormonogenesis as a major cause of primary CH in the entire Indian country in striking contrast with Western data where thyroid dysgenesis is more common.[9]

The increasing social culture and impact of using rock salt and organic salt with absent to varying concentrations of fortified iodine may be linked and warrant focused research studies

for further correlations. [9]

In childhood too, hypothyroidism can occur. In a study from Mumbai, out of 800 children with thyroid disease, 79% had hypothyroidism. Common causes of hypothyroidism in these children were thyroid dysgenesis, dyshormonogenesis, and thyroiditis.[6]

- **Why hypothyroidism is more common in women**

The prevalence of hypothyroidism among women is striking conclusion from various studies. A study done in Guwahati reveals that the higher prevalence of hypothyroidism was found among female gender against their counterpart, 42.27% versus 25%. A hospital-based study done in North Kerala revealed a prevalence of hypothyroidism of 4.2% among adults and the prevalence in female versus male was 4.3% versus 4.05%.[6]

Approximately 1 in 8 women will be affected by a thyroid condition at some point in their lives. The risk for women is about 10 times higher than for men. One reason for this is that thyroid disorders are often triggered by autoimmune responses, which happen when the body‘s immune system starts to attack its own cells. We still don‘t understand what causes these responses, but we do know that autoimmune conditions are more common in women than in men. [16]

Another reason for the prevalence of thyroid disorders in women is that there is an interplay between thyroid hormones and the hormones that fluctuate during the menstrual cycle. Thyroid problems can happen at any time but they are especially common in women during and after the menopause when hormone levels are changing. [16]

- **Role of food habits in hypothyroidism**

According to a community survey in Kerala which was conducted to find out the role of sea foods in the incidence of thyroid disorders, it was found that 11.7 % cases were found positive to thyroid disorders. It is wrongly believed that people residing in coastal area do not suffer from iodine deficiency disorders as they consume sea food which are rich in iodine. Rebecca (1) in her studies showed that the incidence of thyroidism is more in coastal area which might be due to the increase intake of iodine containing foods. Hypothyroidism also is prevalent in this area which may be assosciated to higher intake of iodine rich foods causing

negative feed back mechanism. Use of coconut in their food stuffs may also be a contributing factor in the fluctuation of TSH.[17]

A study was done to know the prevalence of hypothyroidism and its association with anti-TPO antibodies among the adult seafood consuming population in Kerala. It was a hospital-based cross-sectional study involving 300 patients. 30.4% of participants had thyroid dysfunction, prevalence of hypothyroidism and subclinical hypothyroidism was 11.7% and 15%, respectively. Anti-TPO antibody was positive in 71.4% hypothyroid patients and 68.9% subclinical hypothyroid patients. There was a significant relation between hypothyroidism and anti-TPO antibody suggesting thyroid autoimmunity as a risk factor for hypothyroidism.[6]

The prevalence of autoimmune thyroiditis is increased in populations with high dietary iodine, as well as in severely iodine-deficient populations, likely as a result of prolonged thyroid adaptation to iodine intake in both cases. Other environmental factors that have been implicated in autoimmune thyroiditis are deficiencies in vitamin D and selenium.[2]

Ruggeri et al. reported that low consumption of animal foods reduces thyroid autoimmunity and oxidative stress in this disease, while a plant-based diet had positive effects in these patients.[18]

Another study reported that the prevalence and incidence of hypothyroid disease were lower in vegetarians than in omnivores, even after adjusting for confounding factors. Kalicanin et al. documented that there were positive associations between nuts, processed meats, and animal fats in HT patients than in healthy people; however, significant negative relationships were seen between the consumption of whole grains, fruits, vegetable oils, olive oil, red meats, oily fish, soft drinks, and liquor in the case group than in the control group.[19] Another dataset showed that oxidative stress was enhanced in women with HT after pharmacotherapy with levothyroxine, though the daily consumption of vegetables and fruits and maintaining weight within the normal range were effective in reducing their oxidative stress. [20]

Fruits and vegetables, as part of healthy dietary patterns, are rich in fiber, carotene, folate, various phytochemicals/polyphenols, and vitamins B, C, and E. They play antioxidative, anti-inflammatory, and immunomodulatory roles in the body.[20]

Diets rich in selenium may increase the production of active thyroid hormone and reduce

TgAb and TPOAb. The most recent meta-analysis found that the use of selenium supplements reduced serum TPOAb levels after 3, 6, and 12 months in HT patients treated with levothyroxine and after three months in untreated cases. [21] Selenium is an essential trace element that is crucial for the normal functioning of many proteins and enzymes. It is taken from food, mainly meat, grains and seafood. Selenium is important for the functioning of many enzymes (selenoproteins) involved in the synthesis and metabolism of thyroid hormones and protection against oxidative damage.[22]

The possible antithyroid effect of soy-based food (Soy, tofu, edamame, miso and soy milk) has long been of scientifc concern. The goitrogenic compounds found in soy are isofavones, a subclass of favonoids. Isofavones inhibit TPO, an enzyme involved in the synthesis of thyroid hormones.[22]

Life Style and Hypothyroidism

Lifestyle factors that showed the clearest association with TSH and thyroid hormones were smoking, body mass index (BMI) and iodine (micronutrient taken from the diet). Smoking mainly led to a decrease in TSH levels and an increase in triiodothyronine (T3) and thyroxine (T4) levels, while BMI levels were positively correlated with TSH and free T3 levels. Excess iodine led to an increase in TSH levels and a decrease in thyroid hormone levels. Among the pollutants analyzed, most studies observed a decrease in thyroid hormone levels after exposure to perchlorate. They observed that every 10 ng/mL increase in serum cotinine resulted in a 1.4% decrease in TSH levels. It was also observed that TSH levels gradually increased after smoking cessation.[22]

The majority of studies that investigated the influence of body mass index (BMI) on TSH and thyroid hormone levels reported a positive correlation between BMI values and TSH and fT3 levels. The relationship between thyroid hormone levels and weight is well understood in autoimmune disorders. Hyperthyroidism is accompanied by weight loss while hypothyroidism is associated with weight gain. However, the reason for variation in TSH and thyroid hormone levels in euthyroid individuals after an increase in their BMI is not very well understood. Several hypotheses have been proposed. Adipose tissue secretes the hormone leptin which is also involved in the production of Hypothalamic TRH. There is a positive correlation between leptin levels and BMI, so this could be a good explanation for why TSH levels increase with increasing BMI. However, some authors think that changes in TSH levels and levels of thyroid hormones are the cause, not the consequence, of an increase in

BMI. They propose that lower thyroid function can lead to obesity, probably as a result of a lower metabolic rate.[22]

Among thyroid diseases, researchers have to pay attention to the relationship between lifestyle and SCH. Studies have shown that changes in smoking habits could affect the occurrence of clinical hypothyroidism and SCH; iodine deficiency and iodine excess both increase the incidence of overt hypothyroidism and SCH; compared with sleep duration of 7–8 h, shorter and longer sleep duration was associated with an increased risk of SCH; people who were sedentary had higher levels of TSH than those who exercised regularly, and SCH was associated with decreased exercise tolerance. However, there are few studies on how lifestyle affects thyroid function in SCH. Thyroid function is regulated by hypothalamus and pituitary. The changes of thyroid hormone are regulated by the negative feedback of hypothalamus pituitary thyroid (HPT) axis.[22]

Studies have shown that among women with SCH, the average TSH level of smokers is higher than that of non-smokers, and the clinical performance score of smokers shows that their hypothyroidism is more severe. Some studies also suggested that the prevalence of elevated serum TSH was significantly decreased in smokers, and the risk of autoimmune-related hypothyroidism increased significantly after quitting smoking, suggesting that smoking may be a protective factor for hypothyroidism.[23]

- **Socio demographic features related to hypothyroidism**

Differences in iodine status affect the prevalence of hypothyroidism, which occurs more frequently both in populations with a relatively high iodine intake and in severely iodine-deficient populations. Hypothyroidism occurs more frequently in women, in older people (>65 years), and in white individuals, although data on ethnic differences are scarce.[3]

Among people residing in Coastal area were found to have thyroid disorder, whereas people in Non-coastal, Mid land and Hilly area have a low prevalence of thyroid disorder. P Value is 0.0003, which shows that there is a significant linear trend among the categories. It implies that geographical variation is a causative factor for thyroidism. According to Chaturvedi in mountainous and hilly areas iodine content is lost due to years of washing of the soil by heavy rains and recurrent floodings. As a result, all the living things which are depending on the soil directly or indirectly become iodine deficient. The survey conducted by Prema revealed that frequent consumption of tapioca which is a common and favourite dish of

Keralites may be one of the reasons for the prevalence of goitre in Kerala. Tapioca contains hydrocyanic acid which blocks the uptake of iodine by thyroid causing goitre.[17]

On the other hand, compared with coastal cities (eg, Mumbai, Goa, and Chennai), cities located inland (eg, Kolkata, Delhi, Ahmedabad, Bangalore, and Hyderabad) have a higher prevalence (11·7% vs 9·5%).[5]

The prevalence of subclinical and overt hypothy-roidism is generally higher in areas of optimum or chronic excessive iodine intake than in settings of mild-to-moderate iodine deficiency. In the meta-analysis by Weng et al., across 43 Chinese studies, the authors found the highest prevalence of subclinical hypothyroidism in the group with excessive iodine intake compared with the adequate or deficient intake groups (8%, 3%, and 2%,respectively). Another recent meta-analysis of international studies in adults reported an OR for overt and subclinical hypothyroidism of 2.8 (95% CI: 1.5–5.3) and 2.0 (95% CI: 1.6–2.6) between adequate and excessive iodine intakes, respectively. [2]

Even small increase in iodine intake is associated with a small increase in the prevalence of sub-clinical hypothyroidism, particularly if the iodine intake increases from deficient to more than adequate within a short time. In a hospital-based retrospective study of 885 Slovenian adults, an increase in the incidence of iodine-induced hypothyroidism was observed from 5% in 2 years before to 20% in 10 years following a mandatory increase in salt iodization levels from 10 to 25 mg/kg in 1999. The development of hypothyroidism following chronic excess iodine exposure may be due to increased thyroid autoimmunity, the presence of elevated antithyroid antibodies. Excessive iodine consumption has been widely described as a risk factor for the development of thyroid autoimmunity.[4]

The study showed the increased incidence of Hypothyroidism in young women as compared to older women and hyperthyroidism more common in older age group. Excess intake of iodine rich food also leads to hypothyroidism by reverse mechanism.[4]

Out of 18 hypothyroidism patients, 13 (72%) were found to have irregularity in menstrual periods which includes heavy menstruation and cessation of periods for 2- 3 months. Davies in his article explained that hypofunction of thyroid affects ovulation frequency and occurrence. It increases the prolactin level and prevents the ovulation too. Thyroid hormone is essential for egg fertilization. Hypo function of thyroid gland causes infertility.[17]

Environmental factors other than iodine deficiency might play a part in hypothyroidism in India. Goitrogens and exposure to cyanogenic compounds have an adverse impact on iodine metabolism‖, says Mithal. The unregulated use of pesticides and exposure to endocrine disruptors could be a reason‖. –Unclean drinking water and exposure to industrial pollutants like resorcinol and phthalic acid have also been suggested as causes.[5]

A cross-sectional, multi-centered epidemiology study was conducted at eight sites in India namely Bangalore, Chennai, Delhi, Goa, Ahmedabad, Hyderabad, Kolkata and Mumbai. Inland cities showed a higher prevalence of hypothyroidism as compared to coastal cities. Female gender and older age were found to have significant association with hypothyroidism. Kolkata recorded the highest prevalence of hypothyroidism.[24]

Children with Down syndrome are at increased risk – upto 28 times the normal population – for hypothyroidism. Autoimmune predisposition or dysgenesis may contribute to thyroid dysfunction among children with this chromosomal anomaly. In this setting, SCH may warrant treatment as the progression to overt hypothyroidism is more likely. Type 1 diabetes predisposes children to thyroid dysfunction. In a study by Soliman, *et al*., the prevalence of SCH in children (mean age 10 yrs) with type I diabetes was 11.2%. Other conditions which may be associated with elevated risk for SCH include antiepileptic drug usage and coeliac disease.[25]

Hypothyroidism and Lt4 intake

Lifelong replacement therapy with levothyroxine (LT4) is usually the treatment of choice for hypothyroidism. Although LT4 therapy has been established as a safe, cheap, and effective therapy, many studies continue to show that LT4 therapy is not always efficacious in achieving normal thyroid-stimulating hormone (TSH) values in hypothyroid patients.[26]

Many patients under LT4 therapy are either over-treated or under-treated due to drug interactions, malabsorption syndromes, pancreatic and liver disorders, autoimmune gastritis, high fiber diet, and more frequently non-compliance with LT4 therapy. Factors such as age, etiology of hypothyroidism, concomitant medications, and concomitant illnesses, etc. are also known to alter serum TSH levels, stressing the need for individualization of dosage.[26]

Despite TSH concentrations within the reference interval, 5-10% of hypothyroid patients receiving L-T4 report impaired psychological well-being, depression or anxiety. Furthermore,

the presence of so-called brain fog in L-T4 treated hypothyroid patients is a well known phenomenon experienced by many patients. Several mechanisms may underlie the discrepancy between _normal‘ laboratory outcomes and persistent symptoms. Over the last decades, many studies focused on the possible role of low triiodothyronine (T3) during L-T4 treatment. The assumption is that L-T4 substitution alone does not suffce, as it leads to low/low normal (F)T3 and high FT4 concentrations in the presence of TSH concentrations within the reference interval. A recent meta-analysis failed to detect an association between TPO-antibodies and persistent symptoms, although a link between TPO-antibodies and decreased quality of life was suggested. Moreover, (undetected) autoimmune comorbidities, chronic medication use, lifestyle, and unrealistic expectations may play a role in persistence of symptoms as well.[27]

CONCLUSION

There is a large and increasing number of undetected hypothyroidism in the population, affecting the well-being, work efficiency, and productivity of the community, despite iodine sufficiency. Hypothyroidism being an easily tested and treated condition, larger population-based screening studies need to be undertaken. Hypothyroidism is a growing public health concern in India. India is now in post iodization era, where iodine depletion is replaced by iodine sufficiency. Even then, thyroid disorders are increasing, predominantly hypothyroidism. The prevalence of hypothyroidism is 9.6% and there is clear evidence of more prevalence among female against their counterpart. In summary, there is a high burden of thyroid diseases in India. Due to lack of resources, screening for thyroid diseases in the general population is not cost effective. However, ensuring adequate iodine nutrition of pregnant women and children and screening for congenital hypothyroidism are interventions that require a priority in the Indian population. Iodine nutrition should be ensured in all women of reproductive age group especially in areas identified to be endemic for iodine deficiency disease. Congenital hypothyroidism screening for all the new born and establishment of a national screening program can be done.

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