"A Prescription based survey on Prevalence and Management of Thyroid Cancer"

This dissertation is submitted to the Department of Pharmacy, East West University in the partial fulfillment of the requirements for the Degree of Masters of Pharmacy

Submitted By

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Declaration by the Research Candidate

I, **Md. Nayeem Hassan**, ID: 2013-1-79-018, hereby declare that the dissertation entitled

"A Prescription based survey on Prevalence and Management of Thyroid Cancer" submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Masters of Pharmacy, under the supervision and guidance of **Nishat Nasrin**, Senior Lecturer, Department of Pharmacy, East West University, Dhaka, Bangladesh.

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Certificate by the Supervisor

This is to certify that the dissertation entitled "A Prescription based survey on Prevalence and Management of Thyroid Cancer" submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Masters of Pharmacy is a bonafied record of original and genuine research work carried out by **Md. Nayeem Hassan**, ID: 2013-1-79-018 under my supervision and guidance.

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Certificate by the Chairperson

This is to certify that the dissertation entitled "A Prescription based survey on Prevalence and Management of Thyroid Cancer" submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Masters of Pharmacy is a bonafied record of original and genuine research work carried out by **Md. Nayeem Hassan**, ID: 2013-1-79-018, under the supervision and guidance of **Nishat Nasrin**, Senior Lecturer, Department of Pharmacy, East West University and no part of this project has been submitted to other degree.

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This Research paper is

Dedicated

To my beloved Parents

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List of Abbreviation	
mU/l	microunit per milliliter
ng/dl	nanograms per deciliter
Mg	micrograms
pg/d	picograms per day
mIU/l	micro-international unit per milliliter
ATD	Autoimmune thyroid disease
T_3	Triiodothyronine
T_4	Tetraiodothyronine
TSH	Thyroid-stimulating hormone
TRH	Thyrotropin-releasing hormone
TBG	Thyroxine-binding globulin
PTH	Parathyroid hormone
TFT	Thyroid function test
WHO	World Health Organization

Abstract

Thyroid Cancer is one of the major health problems in Bangladesh. Thyroid gland is an important endocrine organ which starts functioning in early fetal life and maintains the level of metabolism in the tissues that is optimal for their normal function and intimately related with physical and mental growth. Thyroid cancer may occur in the form of abnormality in size, shape, structure and function of the gland. The pattern of thyroid disease may vary in different parts of the world and also in different regions of the same country. The data were collected from 500 patients from Nuclear Medicine Departments of BSMMU and Dhaka Medical. The present study was carried out on thyroid patients to see the prevalence of thyroid cancer in male and women. Out of 500 thyroid patients 72% were female and 28% were male. Most of the patients having thyroid cancer were in age between 20-40 years. More than 65% of people lies in between the above mentioned age range. More than 90% patients had elevated TSH level. Around 58% patients having TSH level in between 60-100 mU/L. After 3 months of treatment with Radio Iodine TSH level drastically fall down to 0.01-4.5 mU/L. Thyroid disorder is a common cause for low level of triglyceride level in patients. The present study shows that 74% patients have low level of triglyceride (less than 10mg/dL). The incidence rates of thyroid cancer in both women and men have been increasing in recent years. It is also alarming that most of the people of reproductive age in Bangladesh are suffering from thyroid disorder.

Key words: Thyroid cancer, Prevalence, Thyroid Cancer, Triglyceride, Elevated TSH (Thyroid Stimulating Hormone)

1.1 Overview

Thyroid Cancer is one of the major health problems in Bangladesh. Thyroid gland is an important endocrine organ which starts functioning in early fetal life and maintains the level of metabolism in the tissues that is optimal for their normal function and intimately related with physical and mental growth. A normal functioning thyroid is one of the prerequisites for healthy life. Any deviation from normal needs prompt diagnosis and appropriate treatment. Thyroid disease may occur in the form of abnormality in size, shape, structure and function of the gland. The pattern of thyroid disease may vary in different parts of the world and also in different regions of the same country. Besides iodine deficiency various other factors like genetic, goitrogenic substances and some micronutrient deficiencies may be responsible for thyroid disorders. Autoimmune thyroid disease (ATD) may be one of the important causes for developing thyroid illness (Medicinenet, 2011).

1.2 Thyroid gland

The thyroid gland, or simply the thyroid, is one of the largest endocrine glands in the body, and consists of two connected lobes. The thyroid gland is found in the neck, below the laryngeal prominence (Adam's apple). This is formed by angle of the thyroid cartilage that surrounds the larynx. The thyroid gland controls how quickly the body uses energy, makes proteins, and controls the body's sensitivity to other hormones. It participates in these processes by producing thyroid hormones, the principal ones being triiodothyronine (T_3) and thyroxine (sometimes referred to as tetraiodothyronine (T_4). These hormones regulate the growth and rate of function of many other systems in the body. T_3 and T_4 are synthesized from iodine andtyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis. Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus (EndocrineWeb, 2015).

1.3 Structure and Location

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, lobus dexter (right lobe) and lobus sinister (left lobe), connected via the isthmus. Each lobe is about 5 cm long, 3 cm wide and 2 cm thick (Wikipedia, 2015). The thyroid gland is located in the anterior neck**,** spanning between the C5 and T1 vertebrae. It is

an endocrine gland, divided into two lobes which are connected by an isthmus**.** It lies behind the sternohyoid and sternothyroid muscles, wrapping around the cricoid cartilage and superior tracheal rings. It is inferior to the thyroid cartilage of the larynx. The gland is in visceral compartment of the neck, along with the trachea, esophagus and pharynx. The compartment is bound by pre-tracheal fascia. During development, the thyroid gland initially forms in the floor of the primitive pharynx, near the base of the tongue. It descends down the neck to lie in its adult anatomical position (Teachmeanatomy.info, 2015).

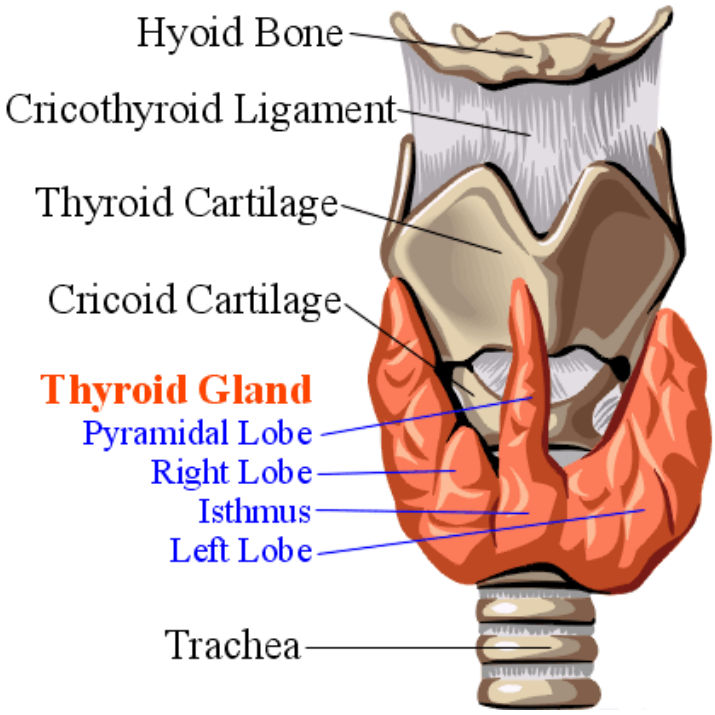

Figure 1.1: Anatomical view of Thyroid gland (Thyroid_Anatomy, 2015)

1.4 Pre-natal development of Thyroid gland

In the embryo, at 3–4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae at a point later indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck, passing

anterior to the hyoid bone. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct.

Thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) start being secreted from the fetal hypothalamus and pituitary at 18-20 weeks of gestation, and fetal production of thyroxine (T_4) reach a clinically significant level at 18–20 weeks. Fetal triiodothyronine (T_3) remains low (less than 15 ng/dL) until 30 weeks of gestation, and increases to 50 ng/dL at term (Pescovitz *et al.*, 2006).

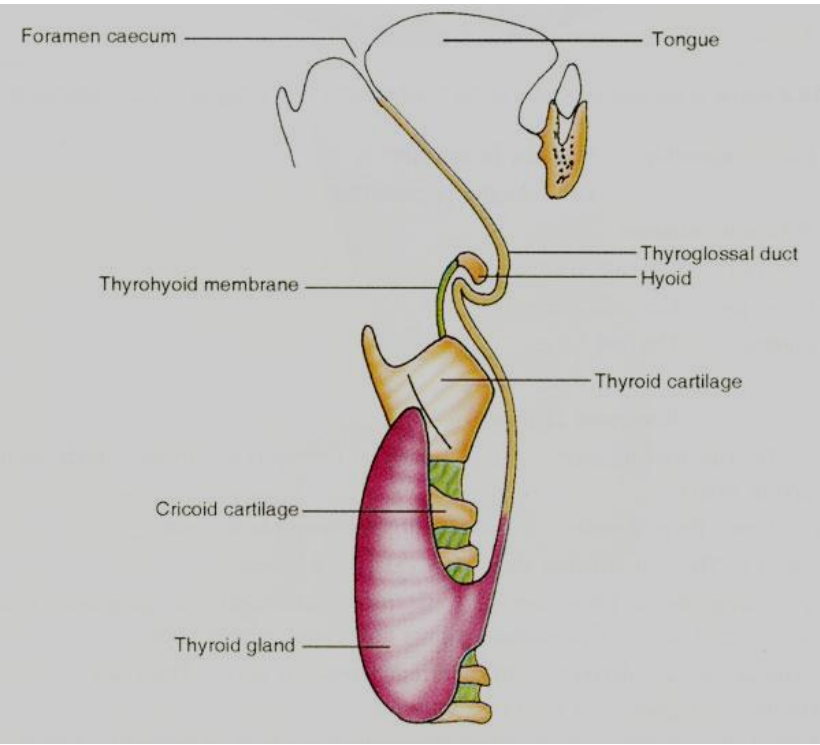

Figure 1.2: Embryonic development of thyroid gland (Anon, 2015)

1.5 Features of Thyroid gland

At the microscopic level, there are three primary features of the thyroid gland and were first discovered by Geoffary Websterson in 1664 (Fawcett *et al.*, 2002).

Table 1.1: Features of Thyroid gland (Fawcett *et al.*, 2002)

Feature	**Description**
Follicles	The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I^-) from the blood for production of thyroid hormones, and also for storage of iodine in thyroglobulin. Twenty-five percent of the body's iodide ions are in the thyroid gland. Inside the follicles, in a region called the follicular lumen, colloid serves as a reservoir of materials for thyroid hormone production. Colloid is rich in a protein called thyroglobulin.
Thyroid epithelial cells (or "follicular cells")	The follicles are surrounded by a single layer of thyroid epithelial cells, which secrete T_3 and T_4. When the gland is not secreting T_3 and T_4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.
Parafollicular cells (or "C cells")	Scattered among follicular cells and in spaces between the spherical follicles is another type of thyroid cell, parafollicular cells, which secrete calcitonin.

1.6 Physiology of Thyroid gland

The thyroid gland produces the hormones L-thyroxine (T4) and L-triiodothyronine (T3), which regulates metabolic body processes, cellular respiration, total energy expenditure, growth and maturation of tissues, and turnover of hormones, substrates, and vitamins (Isselbacher and Harrison, 1995). The gland is composed of a uniform cluster of follicles enclosed by a thin, fibrous capsule surrounded by capillaries. The follicles are the structural, functional, and secretory units of the thyroid gland.

Thyroperoxidase (TPO) is one of the primary enzymes produced in the thyroid. It is synthesized within the endoplasmic reticulum of the thyrocyte and oxidizes iodine, (Miot *et*

al., 2015) thereby facilitating the formation of T3 and T4. Iodine is a critical component of thyroid hormones and composes 65% of T4 weight and 58% of T3 weight. T3 is the active hormone (3 times the metabolic potency of T4), and T4 is the prohormone, broken down in the tissues to form T3 as needed (Miot *et al.*, 2015).

Release of the hormones into the bloodstream involves the negative feedback system of the hypothalamic-pituitary-thyroid axis (Isselbacher and Harrison, 1995). A low metabolic rate or a decrease in serum T3 and/or T4 levels signals the hypothalamus to secrete thyrotropin releasing hormone (TRH), which travels to the anterior pituitary gland and stimulates secretion of thyroid-stimulating hormone (TSH). An elevated T3 serum level inhibits release of TRH and TSH. TSH, in turn, stimulates the thyroid gland to manufacture and release stored T3 and T4 until the metabolic rate is normalized (Isselbacher and Harrison, 1995). Thyroxine-binding globulin (TBG) is the primary protein that binds to T3 and T4 in the plasma. Unbound or free hormones are available to the tissue. The normal range of serum TSH concentration in the euthyroid population was found to be 0.4 to 2.5 mIU/L by the National Academy of Clinical Biochemistry, and supports the redefined TSH reference range (0.3-3.0 mIU/L) recommended by the AACE (Garber *et al.*, 2012).

An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids (Dietrich, 2002).

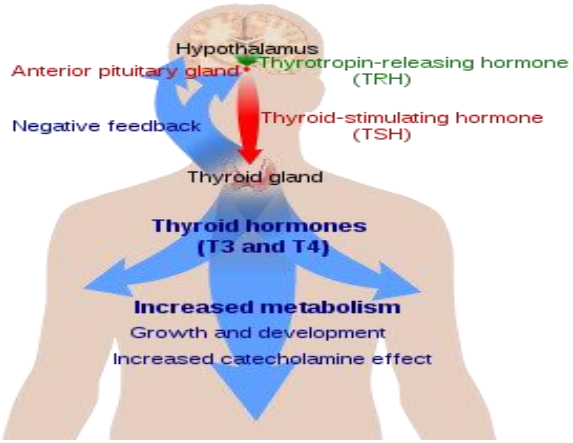

Figure 1.3: Physiology of Thyroid gland (Anon, 2015)

1.7 Thyroid Disorders

Thyroid disorders can range from a small, harm less goiter (enlarged gland) that needs no treatment to life-threatening cancer. The most common thyroid problems involve abnormal production of thyroid hormones (WebMD, 2015). Imbalance in production of thyroid hormones arises from dysfunction of the thyroid gland itself, the pituitary gland, which produces thyroid-stimulating hormone (TSH), or the hypothalamus, which regulates the pituitary gland via thyrotropin-releasing hormone (TRH). Concentrations of TSH increase with age, requiring age-corrected tests (Surks and Hollowell, 2007). Too much thyroid hormone results in a condition known as hyperthyroidism. Insufficient hormone production leads to hypothyroidism.

Thyroid diseases are four types:

- Hyperthyroidism (abnormally increased activity)
- Hypothyroidism (abnormally decreased activity)
- Thyroiditis (inflammation of thyroid gland)
- Thyroid Cancer (which are generally benign thyroid neoplasms (tumours), but may be thyroid cancers)

1.8 Hyperthyroidism

Hyperthyroidism, also known as over active thyroid and hyperthyreosis, is the condition that occurs due to excessive production of thyroid hormone by the thyroid gland. Thyrotoxicosis is the condition that occurs due to excessive thyroid hormone of any cause and therefore includes hyperthyroidism (Fadeyev and Karseladse, 2011). Signs and symptoms vary between people and may include irritability, muscle weakness, sleeping problems, a fast heartbeat, poor tolerance of heat, diarrhea, enlargement of the thyroid, and weight loss. Symptoms are typically less in the old and during pregnancy (Niddk.nih.gov, 2015).

1.8.1 Causes of Hyperthyroidism

There are several causes of hyperthyroidism. Most often, the entire gland is overproducing thyroid hormone. Less commonly, a single nodule is responsible for the excess hormone secretion, called a "hot" nodule. Thyroiditis (inflammation of the thyroid) can also cause

hyperthyroidism (EndocrineWeb, 2015). Functional thyroid tissue producing an excess of thyroid hormone occurs in a number of clinical conditions.

The major causes in human body are (Andersson and Zimmermann, 2010):

- Graves' disease
- Toxic thyroid adenoma
- Toxic multi nodular goiter

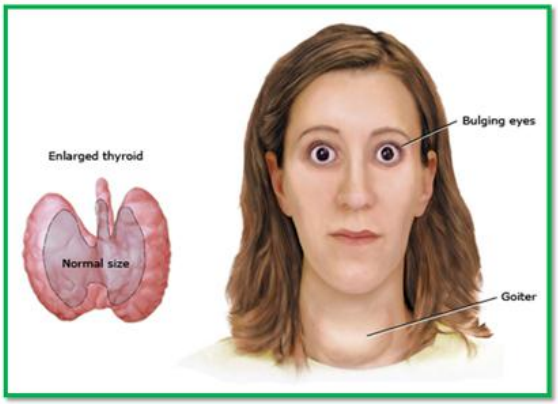

Figure 1.4: Hyperthyroidism (Medicinenet.com, 2015)

1.8.2 Graves Diseases

Graves' disease, also known as toxic diffuse goiter and Flajani-Basedow- Graves' disease, is an autoimmune disease that affects the thyroid. It frequently results in hyperthyroidism and an enlarged thyroid. Signs and symptoms of hyperthyroidism may include irritability, muscle weakness, sleeping problems, a fast heartbeat, poor tolerance of heat, diarrhea, and weight loss. Other symptoms may include thickening of the skin on the shins, known as pretibial myxedema, and eye problems such as bulging, a condition known as Graves' ophthalmopathy. The exact cause is unclear; however, it is believed to involve a combination of genetic and environmental factors. A person is more likely to be affected if they have a family member with the disease. If one twin is affected there is a 30% chance the other twin will also have the disease. The onset of disease may be triggered by stress, infection, or giving birth. Those with other autoimmune diseases such as type 1 diabetes and rheumatoid arthritis are more likely to be affected. Smoking increases the risk of disease and may make the eye problems worse. The disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to thyroid stimulating hormone (TSH). These

antibodies cause the thyroid gland to produce excess thyroid hormone. The diagnosis may be suspected based on symptoms with blood tests and radioiodine uptake used to confirm the disease. Typically blood tests show a raised T_3 and T_4, low TSH, increased radioiodine uptake in all areas of the thyroid, and TSI antibodies (Brent, 2008).

Figure 1.5: Graves' disease (Medicinenet.com, 2015)

1.8.3 Toxic Thyroid Adenoma

A thyroid adenoma is a benign tumor of the thyroid gland. Almost all thyroid adenomas are follicular adenomas.(Fausto *et al*, 2005) Follicular adenomas can be described as "cold", "warm" or "hot" depending on their level of function. Histopathologically, follicular adenomas can be classified according to their cellular architecture and relative amounts of cellularity and colloid into the following types:

- Fetal (micro follicular) - these have the potential for micro invasion. These consist of small, closely packed follicles lined with epithelium.
- colloid (macro follicular) - these do *not* have any potential for micro invasion
- embryonal (atypical) - have the potential for micro invasion.

A thyroid adenoma may be clinically silent ("cold" or "warm" adenoma), or it may be a functional tumor, producing excessive thyroid hormone ("hot" adenoma). In this case, it may result in symptomatic hyperthyroidism, and may be referred to as a toxic thyroid adenoma. (Fernando, 2009)

Figure 1.6: Thyroid adenoma (Medicinenet.com, 2015)

1.8.4 Toxic multi nodular goiter

Toxic multinodular goiter (also known as toxic nodular goiter, toxic nodular struma, or Plummer's disease) is a multinodular goiter associated with a hyperthyroidism. It is a common cause of hyperthyroidism in which there is excess production of thyroid hormones from functionally autonomous thyroid nodules, which do not require stimulation from thyroid stimulating hormone (TSH). (Krohn *et al*., 2005)

It is the second most common cause of hyperthyroidism (after Graves' disease) in the developed world. In countries where the population is iodine-deficient i.e. the developing world, iodine deficiency is the most common cause of hypothyroidism. (Decreased iodine leads to decreased thyroid hormone.) However, iodine deficiency can cause goitre (thyroid enlargement); within a goiter, nodules can develop. Risk factors for toxic multinodular goiter include individuals over 60 years of age and being female.

Symptoms of toxic multinodular goitre are similar to that of hyperthyroidism, including:

1. heat intolerance
2. muscle weakness/wasting
3. hyperactivity
4. fatigue

5. tremor
6. irritability
7. weight loss
8. osteoporosis
9. increased appetite
10. non-painful goitre (swelling of the thyroid gland)
11. tachycardia (high heart rate - above 100 beats per minute at rest in adults)
12. toxic multinodular goiter can be treated with antithyroid medications such as propylthiouracil or methimazole, radioactive iodine, or with surgery. (Freitas, 2000)

1.9 Hypothyroidism

Hypothyroidism often called underactive thyroid or low thyroid and sometimes hypothyreosis, is a common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone. Worldwide, too little iodine in the diet is the most common cause of primary hypothyroidism (Garber *et al.*, 2012).

1.9.1 Sign and symptoms of Hypothyroidism

People with hypothyroidism often have no or only mild symptoms. Numerous symptoms and signs are associated with hypothyroidism, and can be related to the underlying cause, or a direct effect of having not enough thyroid hormones. Hashimoto's thyroiditis may present with the mass effect of a goiter (enlarged thyroid gland). (Khandelwal and Tendon, 2012)

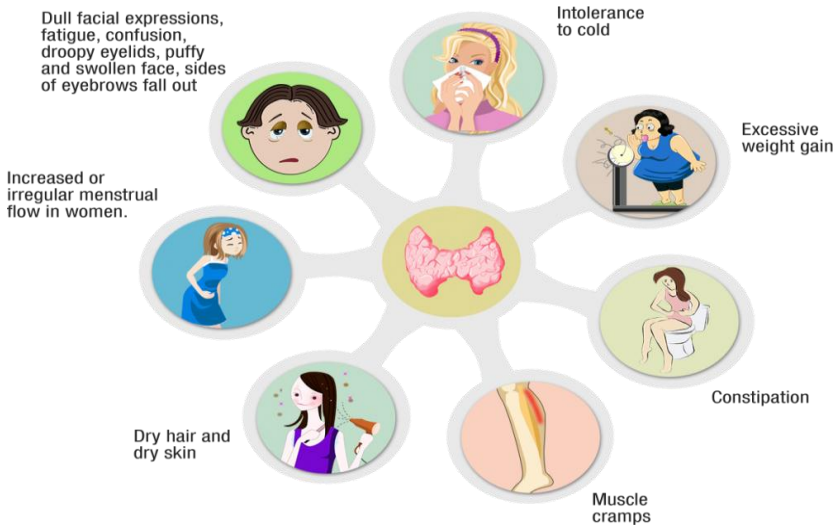

Figure 1.7: Symptoms of Hypothyroidism (Medicinenet.com, 2015)

1.9.2 Causes of Hypothyroidism (Medicinenet.com, 2015)

- Congenital thyroid abnormalities (Thyroid deficiency at birth)
- Autoimmune disorders such as Hashimoto's thyroiditis
- Iodine deficiency (more likely in poorer countries)
- Removal of the thyroid following surgery to treat severe hyperthyroidism and/or thyroid cancer

1.9.3 Congenital Hypothyroidism

Congenital hypothyroidism (CH) or cretinism is a condition of thyroid hormone deficiency present at birth. Approximately 1 in 4000 newborn infants has a severe deficiency of thyroid function, while even more have mild or partial degrees. If untreated for several months after birth, severe congenital hypothyroidism can lead to growth failure and permanent intellectual disability. Treatment consists of a daily dose of thyroid hormone (thyroxine) by mouth. Because the treatment is simple, effective, and inexpensive, nearly all of the developed world practices newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. Around the world, the most common cause of congenital hypothyroidism is iodine deficiency, but in most of the developed world and areas of adequate environmental iodine, cases are due to a combination of known and unknown causes. Most commonly there is a defect of development of the thyroid gland itself, resulting in an absent (athyreosis) or underdeveloped (hypoplastic) gland. A hypoplastic gland may develop higher in the neck or even in the back of the tongue. A gland in the wrong place is referred to as *ectopic*, and an ectopic gland at the base or back of the tongue is a *lingual* thyroid. (Nagayama *et al*., 2007**)**

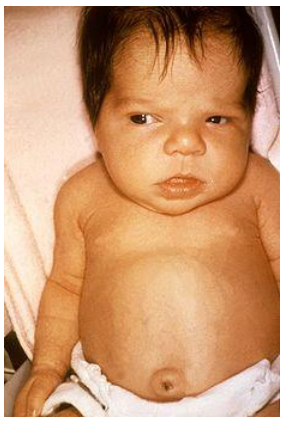

Figure 1.8: Congenital Hypothyroidism (Medicinenet.com, 2015)

1.9.4 Hashimoto's thyroiditis

Hashimoto's thyroiditis or chronic lymphocytic thyroiditis is an autoimmune disease in which the thyroid gland is attacked by a variety of cell- and antibody-mediated immune processes, causing primary hypothyroidism. It was the first disease to be recognized as an autoimmune disease. (Garber *et al*., 2012)

There are many symptoms that are attributed to Hashimoto's thyroiditis or Hashimoto's disease. The most common symptoms include the following: fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, panic disorder, a slowed heart rate, and problems getting pregnant and maintaining pregnancy.

Hashimoto’s disease is about seven times more common in women than in men. It can occur in teens and young women, but more commonly shows up in middle age, particularly for men. People who develop Hashimoto’s disease often have family members who have thyroid or other autoimmune diseases, and sometimes have other autoimmune diseases themselves. (Vaidya, Chakera and Pearce, 2011)

1.9.5 Iodine deficiency

Iodine deficiency is a lack of the trace element iodine. It may result in goiter (so-called endemic goiter), as well as cretinism, which results in developmental delays and other health problems. Iodine deficiency is an important public health issue as it is a preventable cause of intellectual disability.

Iodine is an essential trace element; the thyroid hormones thyroxine and triiodothyronine contain iodine. In areas where there is little iodine in the diet—typically remote inland areas where no marine foods are eaten, iodine deficiency is common. It is also common in mountainous regions of the world where food is grown in iodine-poor soil.

Prevention includes adding small amounts of iodine to table salt — a product known as iodized salt. Iodine compounds have also been added to other foodstuffs, such as flour, water and milk in areas of deficiency. Seafood is also a well known source of iodine.

Iodine deficiency resulting in goiter occurs in 187 million people globally as of 2010 (2.7% of the population). It resulted in 2700 deaths in 2013 up from 2100 deaths in 1990. (Knudsen *et al*., 2002)

Following is a list of potential risk factors that may lead to iodine deficiency:

1. Low dietary iodine
2. Selenium deficiency
3. Pregnancy
4. Exposure to radiation
5. Increased intake/plasma levels of goitrogens, such as calcium
6. Gender (higher occurrence in women)
7. Smoking tobacco
8. Alcohol (reduced prevalence in users)
9. Oral contraceptives (reduced prevalence in users)
10. Perchlorates
11. Thiocyanates
12. Age (for different types of iodine deficiency at different ages)

1.10 Thyroiditis

Thyroiditis is the inflammation of the thyroid gland. Thyroiditis is generally caused by an attack on the thyroid, resulting in inflammation and damage to the thyroid cells. This disease is often considered a malfunction of the immune system. It can also be caused by an infection, like a virus or bacteria, which works in the same way as antibodies to cause inflammation in the glands. Certain people make thyroid antibodies, and thyroiditis can be considered an autoimmune disease, because the body acts as if the thyroid gland is foreign tissue (Robert Ferry Jr., 2015). Some drugs, such as interferon and amiodarone, can also cause thyroiditis because they have a tendency to damage thyroid cells.

1.11 Thyroid Cancer

Thyroid cancer is a cancer originating from follicular or parafollicular thyroid cells. These cells give rise to both well-differentiated cancers (i.e., papillary and follicular) and anaplastic thyroid cancer. The second cell type, the C or parafollicular cell, produces the hormone calcitonin and is the cell of origin for medullary thyroid carcinoma (MTC). (Carling and Udelsman, 2014).

Thyroid cancers are thought to be related to a number of environmental and genetic predisposing factors, but significant uncertainty remains regarding its causes.

Environmental exposure to ionizing radiation from both natural background sources and artificial sources is suspected to play a significant role, and there are significant increased rates of thyroid cancer in those exposed to mantlefield radiation for lymphoma, and those exposed to iodine-131 (National Cancer Institute, 2015).

Genetic causes include multiple endocrine neoplasia type 2 which markedly increases rates, particularly of the rarer medullary form of the disease (National Cancer Institute, 2015).

Thyroid cancers can be classified according to their histopathological characteristics. The following variants can be distinguished (distribution over various subtypes may show regional variation): (National Cancer Institute Information Service, 2007)

- Papillary thyroid cancer (75% to 85% of cases) – often in young females – excellent prognosis. May occur in women with familial adenomatous polyposis and in patients with Cowden syndrome.
- Follicular thyroid cancer (10% to 20% of cases); occasionally seen in patients with Cowden syndrome
- Medullary thyroid cancer (5% to 8% of cases)- cancer of the parafollicular cells, often part of multiple endocrine neoplasia type 2.
- Poorly differentiated thyroid cancer
- Anaplastic thyroid cancer (less than 5% of cases) is not responsive to treatment and can cause pressure symptoms

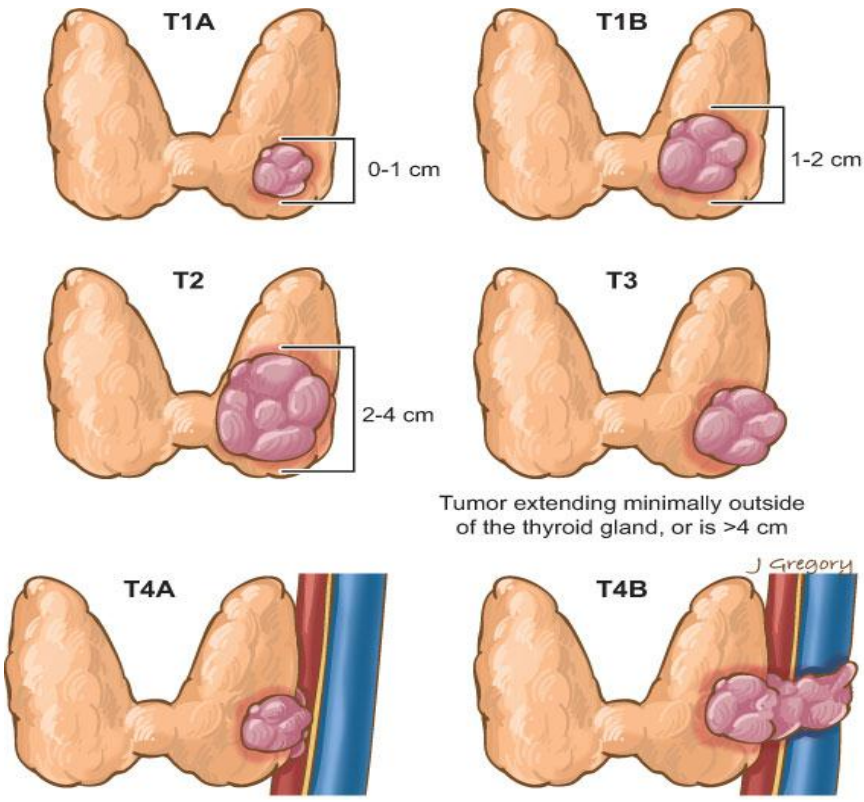

Figure 1.9: Different stages of Thyroid cancer (Medicinenet.com, 2015)

➢ **T1a**	➢ The tumor is 1 centimeter or less and completely within the thyroid gland.
➢ **T1b**	➢ The tumor is between 1 and 2 centimeters and limited to the thyroid gland.
➢ **T2**	➢ The tumor is between 2 and 4 centimeters and limited to the thyroid gland.
➢ **T3**	➢ The tumor is more than 4 centimeters and limited to the thyroid gland or any tumor that has minimal extension outside of the thyroid gland.
➢ **T4a**	➢ Moderately advanced disease: The tumor is any size but extends beyond the thyroid capsule to invade the subcutaneous tissue, larynx, trachea, esophagus or recurrent laryngeal nerve.
➢ **T4b**	➢ Very advanced disease: The tumor invades the pre-vertebral fascia or surrounds the carotid artery or major chest vessels.

1.12 Diagnosis of Thyroid Disorder

Thyroid function tests (TFTs) is a collective term for blood tests used to check the function of the thyroid (Dayan, 2001). TFTs may be requested if a patient is thought to suffer from hyperthyroidism (overactive thyroid) or hypothyroidism (underactive thyroid), or to monitor the effectiveness of either thyroid-suppression or hormone replacement therapy. A

TFT panel typically includes thyroid hormones such as thyroid-stimulating hormone (TSH, thyrotropin) and thyroxine (T4), andtriiodothyronine (T3) depending on local laboratory policy.

Table 1.2: Thyroid Function Test (EndocrineWeb, 2015)

Test	**Abbreviation**	**Normal ranges**
Thyroid-stimulating hormone	TSH	0.5–6.0 μU/ml
Free thyroxine	FT_4	7–18 ng/l = 0.7–1.8 ng/dl
Serum triiodothyronine	T_3	0.8–1.8 μg/l = 80–180 ng/dl
Radioactive iodine-123 uptake	RAIU	10–30%
Free thyroxine fraction	FT_4F	0.03–0.005%
Serum thyroxine	T_4	46–120 μg/l = 4.6–12.0 μg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT_4I	4–11
Free triiodothyronine l	FT_3	230–619 pg/d
Free T3 Index	FT_3I	80–180

Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 µg
TRH stimulation test	Peak TSH	9–30 µIU/ml at 20–30 min.
Serum thyroglobulin l	Tg	0-30 ng/m

- µU/ml = mU/l, microunit per milliliter
- ng/dl, nanograms per deciliter
- µg, micrograms
- pg/d, picograms per day
- µIU/ml = mIU/l, micro-international unit per milliliter

1.12.1 Major Tests (American Thyroid Association, 2015)

Blood tests to measure TSH, T4, T3 and Free T4 are readily available and widely used. Tests to evaluate thyroid function include the following:

1.12.2 TSH tests

The best way to initially test thyroid function is to measure the TSH level in a blood sample. A high TSH level indicates that the thyroid gland is failing because of a problem that is directly affecting the thyroid (primary hypothyroidism). The opposite situation, in which the TSH level is low, usually indicates that the person has an overactive thyroid that is producing too much thyroid hormone (hyperthyroidism). Occasionally, a low TSH may result from an abnormality in the pituitary gland, which prevents it from making enough TSH to stimulate the thyroid (secondary hypothyroidism). In most healthy individuals, a normal TSH value means that the thyroid is functioning normally.

1.12.3 T4 tests

T4 circulates in the blood in two forms:

1) T4 bound to proteins that prevent the T4 from entering the various tissues that need thyroid hormone.

2) Free T4, which does enter the various target tissues to exert its effects. The free T4 fraction is the most important to determine how the thyroid is functioning, and tests to measure this are called the Free T4 (FT4) and the Free T4 Index (FT4I or FTI). Individuals who have hyperthyroidism will have an elevated FT4 or FTI, whereas patients with hypothyroidism will have a low level of FT4 or FTI.

Combining the TSH test with the FT4 or FTI accurately determines how the thyroid gland is functioning.

The finding of an elevated TSH and low FT4 or FTI indicates primary hypothyroidism due to disease in the thyroid gland. A low TSH and low FT4 or FTI indicates hypothyroidism due to a problem involving the pituitary gland. A low TSH with an elevated FT4 or FTI is found in individuals who have hyperthyroidism.

1.12.4 T3 tests

T3 tests are often useful to diagnosis hyperthyroidism or to determine the severity of the hyperthyroidism. Patients who are hyperthyroid will have an elevated T3 level. In some individuals with a low TSH, only the T3 is elevated and the FT4 or FTI is normal. T3 testing rarely is helpful in the hypothyroid patient, since it is the last test to become abnormal. Patients can be severely hypothyroid with a high TSH and low FT4 or FTI, but have a normal T3. In some situations, such as during pregnancy or while taking birth control pills, high levels of total T4 and T3 can exist. This is because the estrogens increase the level of the binding proteins. In these situations, it is better to ask both for TSH and free T4 for thyroid evaluation.

1.12.5 Thyroid antibody tests

The immune system of the body normally protects us from foreign invaders such as bacteria and viruses by destroying these invaders with substances called antibodies produced by blood cells known as lymphocytes. In many patients with hypothyroidism or hyperthyroidism, lymphocytes make antibodies against their thyroid that either stimulate or damage the gland.

Two common antibodies that cause thyroid problems are directed against thyroid cell proteins: thyroid peroxidase and thyroglobulin. Measuring levels of thyroid antibodies may help diagnose the cause of the thyroid problems. For example, positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in a patient with hypothyroidism make a diagnosis of Hashimoto's thyroiditis. If the antibodies are positive in a hyperthyroid patient, the most likely diagnosis is autoimmune thyroid disease.

1.12.6 Thyroglobulin tests

Thyroglobulin (Tg) is a protein produced by normal thyroid cells and also thyroid cancer cells. It is not a measure of thyroid function and it does not diagnose thyroid cancer when the thyroid gland is still present. It is used most often in patients who have had surgery for thyroid cancer in order to monitor them after treatment. Tg is included in this brochure of thyroid function tests to communicate that, although measured frequently in certain scenarios and individuals, Tg is not a primary measure of thyroid hormone function.

1.13 Global Epidemiology of Thyroid Disease

There were an estimated 14.1 million cancer cases around the world in 2012, of these 7.4 million cases were in men and 6.7 million in women by World Cancer Research Fund International. Thyroid cancer was the most growing cancer worldwide contributing 3% of the total number of new cases diagnosed in 2012 (Aoki *et al.*, 2012).

Up to 300 million people worldwide experience problems with their thyroid, although over half are presumed to be unaware of their condition. Many patients remain undiagnosed with thyroid problems and suffer for a long time as their symptoms have been confused with other conditions, such as depression, pregnancy or the menopause. However, it is important to remember that thyroid dysfunction can be confirmed by doctor through a simple blood test to check the level of thyroid stimulating hormone (TSH) and thyroid hormones in our blood. The National Health and Nutrition Examination Survey (NHANES 1999-2002) of 4392 individuals reflecting the US population reported hypothyroidism (defined as TSH levels exceeding 4.5 mIU/L) in 3.7% of the population (Aoki *et al.*, 2012).

Hypothyroidism is more common in women with small body size at birth and low body mass index during childhood. Iodine deficiency as a cause of hypothyroidism is more common in less-developed countries. Routine supplementation of salt, flour, and other food staples with

iodine has decreased the rates of iodine deficiency. World Health Organization (WHO) data from 130 countries taken from January 1994 through December, 2006 found inadequate iodine nutrition in 30.6% of the population. The WHO recommends urinary iodine concentrations between 100 and 199 μg/L in the general population and a range of 150-249 μg/L in pregnant women (Kajantie *et al.*, 2006). In developed countries, death caused by hypothyroidism is uncommon. It is believed that around 10% of the Bangladeshi people suffer from clinically evident thyroid disorders. Recently subclinical hypo and hyperthyroidisms are included as thyroid disorders adding another 10% population to be dysthyroid totalling 20% of the population suffering from any type of thyroid disorders (Sawin, 1985). Thyroid cancer, in 2010, resulted in 36,000 deaths globally up from 24,000 in 1990. Obesity may be associated with a higher incidence of thyroid cancer, but this relationship remains the subject of much debate. Thyroid cancer accounts for less than 1% of cancer cases and deaths in the UK. Around 2,700 people were diagnosed with Thyroid cancer in the UK in 2011, and around 370 people died from the disease in 2012. (Monzani *et al*., 2012)

In large population-based studies in Western countries with sufficient dietary iodine, 0.3–0.4% of the population has overt hypothyroidism. A larger proportion, 4.3–8.5%, has subclinical hypothyroidism. Of people with subclinical hypothyroidism, 80% have a TSH level below the 10 mIU/l mark regarded as the threshold for treatment. Children with subclinical hypothyroidism often return to normal thyroid function, and a small proportion develops overt hypothyroidism (as predicted by evolving antibody and TSH levels, the presence of celiac disease, and the presence of a goiter). (Bona, Prodam and Monzani, 2012)

Most hypothyroidism is primary in nature. Central/secondary hypothyroidism affects 1:20,000 to 1:80,000 of the population, or about one out of every thousand people with hypothyroidism

Women are more likely to develop hypothyroidism than men. In population-based studies, women were seven times more likely than men to have TSH levels above 10 mU/l. 2–4% of people with subclinical hypothyroidism will progress to overt hypothyroidism each year. The risk is higher in those with antibodies against thyroid peroxidase. Subclinical hypothyroidism is estimated to affect approximately 2% of children; in the adults subclinical hypothyroidism is more common in the elderly, and in Caucasians.

1.13.1 Age-related demographics

The frequency of hypothyroidism, goiters, and thyroid nodules increases with age. Hypothyroidism is most prevalent in elderly populations, with 2-20% of older age groups having some form of hypothyroidism. The Framingham study found hypothyroidism (TSH > 10 mIU/L) in 5.9% of women and 2.4% of men older than 60 years (Sawin, 1985). In NHANES 1999-2002, the odds of having hypothyroidism were 5 times greater in persons aged 80 years and older than in individuals aged 12-49 years.

1.13.2 Sex-related demographics

Community studies use slightly different criteria for determining hypothyroidism; therefore, female-to-male ratios vary. Generally, thyroid disease is much more common in females than in males, with reported prevalence ranging from 2 to 8 times higher in females.

1.13.3 Race-related demographics

The prevalence of hypothyroidism (including the subclinical form) was higher in whites (5.1%) and Mexican Americans than in African Americans (1.7%). African Americans tend to have lower median TSH values.

Thyroid carcinoma is the most common of the endocrine cancers, with annual incidence rates ranging from 1 to 10 cases per 100,000 population, and (other than skin cancer) it accounts for 1.7% of all malignancies in the USA (0.85% of cancers in men, 2.6% in women) (Jemal *et al.*, 2006). Worldwide, incidence rates of thyroid cancer may vary widely, with the causes potentially related to inherent racial or ethnic differences, geographical or environmental differences including iodine excess or deficiency, and possible radiation exposure.

1.14 Risk group of Thyroid disease (American Thyroid Association, 2015)

- Women are generally prone to develop hypothyroidism, but especially during puberty, first menstruation, pregnancy, within the first six months after giving birth, and during menopause
- The elderly generation
- People that have relatives with autoimmune thyroid disorders

- People with autoimmune disease such as type 1 diabetes or rheumatism
- People with manic-depression
- Patients after radiation treatment
- The Caucasian (white) and Asian population

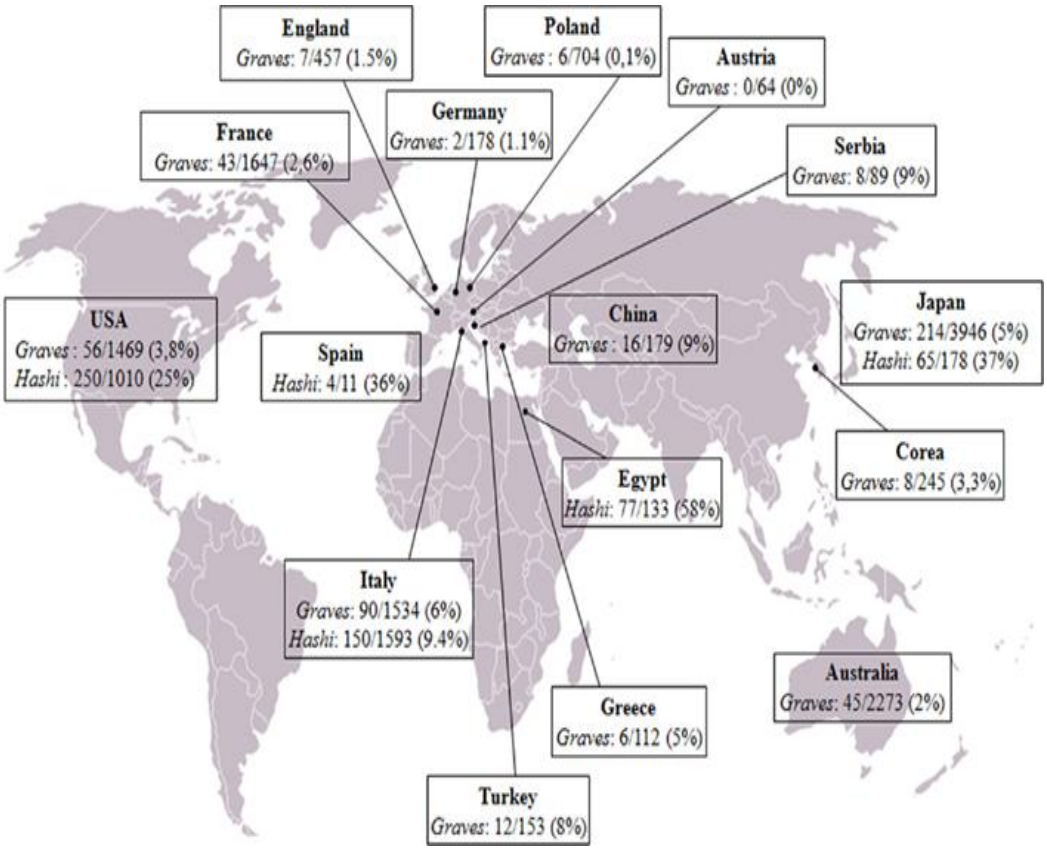

Figure 1.10: Worldwide prevalence of Thyroid patient with *Graves'* disease and *Hashimoto thyroiditis* (Fugazzola *et al.*, 2011)

1.15 Treatment of Thyroid Disorder (WebMD Boots, 2015)

Treatments for thyroid disorders stemming from the over- or underproduction of thyroid hormones rely mainly on medicines and surgery. Treating hyperthyroidism involves suppressing the manufacture of thyroid hormone, while hypothyroidism calls for hormone replacement. Conventional medicine offers extremely effective techniques for lowering,

eliminating or supplementing hormone production. Before deciding treatment doctor will make an evaluation based on patient's particular thyroid condition as well as age, general health and medical history.

1.16 Treatments for Hyperthyroidism

Thyroid hormone production can be suppressed or halted completely in these ways:

- Radioiodine treatment (a form of radiotherapy)
- Anti-thyroid medication
- Surgery

1.16.1 Radioiodine treatment

Radioactive Iodine I-131 (also called Radioiodine I-131) therapy is a treatment for an overactive thyroid, a condition called hyperthyroidism. Hyperthyroidism can be caused by Graves' disease, in which the entire thyroid gland is overactive, or by nodules within the gland which are locally overactive in producing too much thyroid hormone. Radioactive iodine (I-131), an isotope of iodine that emits radiation, is used for medical purposes. When a small dose of I-131 is swallowed, it is absorbed into the bloodstream in the gastrointestinal (GI) tract and concentrated from the blood by the thyroid gland, where it begins destroying the gland's cells.

1.16.2 Antithyroid medications

Anti-thyroid medications are a common treatment for hyperthyroidism, particularly an ongoing form of hyperthyroidism caused by Graves' disease or a goiter. The goal of antithyroid medications is to prevent the thyroid from producing excess amounts of hormone. Though the medications work essentially the same way, they each have their own unique merits and drawbacks.

1.16.3 Propylthiouracil

One of the advantages of PTU is that it has a lower risk of birth defects and therefore it is the first line treatment for pregnant women. A disadvantage is that PTU is only available in 50-milligram units. Patients need to take it in three equal doses, approximately 8 hours apart, each day. According to the American Thyroid Association clinical guidelines, daily dosage

varies from 100 to 600 milligrams, depending on the seriousness of patient's condition and age. This information is general, as dosing varies from patient to patient.

1.16.4 Carbimazole

Carbimazole is used to treat hyperthyroidism. Carbimazole is a pro-drug as after absorption it is converted to the active form, methimazole. Methimazole prevents thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4 (thyroxine).

1.16.5 Side effects of Antithyroid drug

Adverse reactions to antithyroid medications are uncommon (affecting only 1-3% of patients), but they do occur. These side effects include rash, itching, abnormal hair loss, and fever. Less common side effects include nausea, swelling, heartburn, muscle and joint aches, numbness, and headache. In very rare instances, both drugs can cause liver damage. In the most severe of cases, this can result in death.

1.17 Treatment of Hypothyroidism

Hypothyroidism calls for a lifelong regimen of thyroid hormone replacement. No surgical techniques or conventional medicines can boost the thyroid's hormone production once it slows down.

Although hormones from animal extracts are available, doctors generally prescribe synthetic forms of thyroid hormone, such as Levothyroxine. Side effects are rare, but some people experience nervousness or chest pain while taking these medicines. Usually adjusting the levels of medication will alleviate any unpleasant effects.

1.18 Treatment of Thyroiditis

Although sub acute thyroiditis can bring on temporary hyperthyroidism, this condition usually does not require medical treatment. Any pain associated with the inflamed thyroid

can generally be relieved with paracetamol or ibuprofen. If over-the-counter medicines don't help, doctor may prescribe other anti-inflammatory medication for a short period of time.

1.19 Treatment of Thyroid cancer

Thyroid cancer is usually treated by removing surgically either the cancerous tissue or the whole thyroid gland, a procedure known as a thyroidectomy. If the cancer has spread beyond the thyroid, any other affected tissue, such as the lymph glands in the neck, will also be removed. Other forms of therapy may also be used, normally as an adjunct to surgery. These include radioiodine therapy, radiotherapy or chemotherapy, depending on the type of cancer and how much it has spread.

2.1 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey

Outcomes in terms of morbidity and mortality were determined for over 97% of the original sample. The mean Incidence (with 95% confidence Intervals) of spontaneous hypothyroidism in women was 3.5/1000 survivors/year (2.8-4.5) rising to 4.1/1000 survivors/year (3.3-5.0) for all causes of hypothyroidism and in men was 0.6/1000 survivors/year (0.3-1.2). The mean incidence of hyperthyroidism in women was 0.8/1000 survivors/year (0.5.1.4) and was negligible in men. Similar incidence rates were calculated for the deceased subjects. An estimate of the probability of the development of hypothyroidism and hyperthyroidism at a particular time, i.e. the hazard rate, showed an Increase with age in hypothyroidism but no age relation in hyperthyroidism.

The frequency of goitre decreased with age with 10% of women and 2% of men having goitre at follow-up, as compared to 23% and 5% in the same subjects respectively at the first survey. The presence of goitre at either survey was not associated with any clinical or biochemical evidence of thyroid dysfunction. In women, an association was found between the development of a goitre and thyroid-antibody status at follow-up, but not initially. The risk of having developed hypothyroidism at follow-up was examined with respect to risk factors Identified at first survey. The odds ratios (with 95% confidence Intervals) of developing hypothyroidism with (a) raised serum TSH alone were 8 (3-20) for women and 44 (19-104) for men; (b) positive anti-thyroid antibodies alone were 8 (5-15) for women and 25 (10-63) for men; (c) both raised serum TSH and positive anti-thyroid antibodies were 38 (22-65) for women and 173 (81-370) for men (Vanderpump *et al*., 1995).

2.2 The prevalence of thyroid disorders in a middle-aged female population, with special reference to the solitary thyroid nodule

A survey of thyroid disease was conducted in 477 middle-aged women selected at random in the USA where goiter is not endemic. The overall occurrence of thyroid disease was estimated to be 16.2%. Previously known disease was reported by 6.7% of those surveyed, and an additional 9.5% were diagnosed in the present study. The prevalence of all goiter was

11.3%, and of a palpable solitary nodule, 6.5%. Women with goiter were examined by thyroid scintigraphy and fine-needle aspiration cytology. The results of these examinations combined with the conventional clinical examination were considered a sufficient basis for benign diagnosis in all cases except one, a woman with a solitary nodule who was surgically treated because the cytologic report indicated follicular neoplasm; histopathology, however, revealed colloid goiter. The accumulated incidence of hyperthyroidism was 2.3% and of hypothyroidism 0.8%. It is concluded that goiter is a common disorder among women living in non-endemic areas, and that most goiter, including palpable solitary nodules, can be classified after evaluation as multinodular goiter (Christensen *et al*., 1984).

2.3 Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom

Increasing use of assays for TSH with improved sensitivity as a first-line test of thyroid function has raised questions regarding prevalence and clinical significance of abnormal results, especially values below normal. Here assessed the thyroid status of 1210 patients aged over 60 registered with a single general practice by measurement of serum TSH using a sensitive assay. High TSH values were more common in females (11.6%) than males (2.9%). TSH values below normal were present in 6.3% of females and 5.5% of males, with values below the limit of detection of the assay present in 1.5% of females and 1.4% of males. Anti-thyroid antibodies were found in 60% of those with high TSH but only 5.6% of those with subnormal TSH. Eighteen patients were hypothyroid (high TSH, low free thyroxine) and one thyrotoxic (low TSH, raised free thyroxine) at initial testing. Seventy-three patients with elevated TSH but normal free T4 were followed for 12 months; 13 (17.8%) developed low free T4 levels and commenced thyroxine, TSH returned to normal in four (5.5%) and 56 (76.7%) continued to have high TSH values. Sixty-six patients with TSH results below normal were followed. Of the 50 subjects with low but detectable TSH at initial testing, 38 (76%) returned to normal at 12 months; of those 16 with undetectable TSH followed, 14 (87.5%) remained low at 12 months. Only one subject (who had an undetectable TSH) developed thyrotoxicosis. In view of the marked prevalence of thyroid dysfunction in the elderly, we suggest that screening of all patients over 60 should be considered. It is important that those with high TSH are followed in view of the risk of progression to overt hypothyroidism, but the risk of thyrotoxicosis in those with TSH values below normal appears small (Fade *et al*., 1991).

2.4 Thyroid disorders in India: An epidemiological perspective

Thyroid diseases are common worldwide. In India too, there is a significant burden of thyroid diseases. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases. This review will focus on the epidemiology of five common thyroid diseases in India: (1) hypothyroidism, (2) hyperthyroidism, (3) goiter and iodine deficiency disorders, (4) Hashimoto's thyroiditis, and (5) thyroid cancer. 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%.The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%. The prevalence of subclinical hypothyroidism increased with age. About 53% of subjects with subclinical hypothyroidism were positive for anti-TPO antibodies. This was a population-based study, which used cluster sampling strategy. In this study, Urinary Iodine Status was studied in 954 subjects from the same population sampled, and the median value was 211 μg/l; this suggested that this population was iodine sufficient. The prevalence of hyperthyroidism has been studied in several studies. In an epidemiological study from Cochin, subclinical and overt hyperthyroidism was present in 1.6% and 1.3% of subjects participating in a community survey. In a hospital-based study of women from Pondicherry, subclinical and overt hyperthyroidism was present in 0.6% and 1.2% of subjects. Among these patients, the NCRP noted 5614 cases of thyroid cancer, and this included 3617 females and 2007 males (Unnikrishnan and Menon, 2011).

2.5 The prevalence of thyroid dysfunction in a population with borderline iodine deficiency in South Asia

In a cross-sectional study of a random sample of the general population with borderline iodine deficiency was 2656 (65%) of 4073 men and women aged 41 to 71 years participated. Records were made of previous thyroidal illness. Blood samples were drawn for thyroid parameters and TPO Ab values. Iodine and Creatinine was assessed in casual urine samples. Previous or present hyperthyroidism was reported by 1.4% of the participants whereas 0.6% had unknown biochemical hyperthyroidism. All cases of undiagnosed hyperthyroidism were

among women. Previously diagnosed and treated hypothyroidism was reported by 1.0% and undiagnosed hypothyroidism was found in 0.4%. Subclinical hyperthyroidism was found in 1.3% and subclinical hypothyroidism in 0.7%. TPO Ab titres >200 kU/l were found in 16.9% of the women and 6.6% of the men, and 83% of participants with TSH >5 mU/l had TPO Ab titres >200 kU/l. Participants with TPO Ab titres between 100 and 200 kU/l had no increased frequency of thyroid dysfunction. The median iodine excretion rate was estimated as 103 μg/day. Serum TSH values were higher in women than in men and showed higher dispersion in women as well as in old age. Serum free T3 was found to be higher in women than in men and increased with age. Serum free T4 showed no sex difference but values increased with increasing age (Knudsen *et al*., 1999).

2.6 Thyroid Dysfunction in Eastern Nepal

In the present study, it was found that a number of female subjects sent for TFTs was nearly five times that of the males and that goiter was more prevalent in females. This indicates that thyroid disorders are more common in females in Nepal. The distribution of hyper-, hypo-, and euthyroidism among males and females was not significantly different. The most common presentation of IDD is hypo- or euthyroid goiter. Approximately 17% of the subjects screened were hypothyroid and 10.7% of them, *ie*, 1.8% of the subjects tested were found to have sub-clinical disease. This high prevalence of hypothyroidism is a reflection of the persistence of iodine deficiency in the population. Owing to the fact that the management of sub-clinical cases is controversial, and because of financial constraints, these cases need to be followed-up regularly and advised to take iodized salt. The study showed that a substantial number of cases (13.68%) sent for TFTs had hyperthyroidism. The distribution of hyperthyroidism in subjects with goiter was yet higher (27%), and there was no difference in the distribution of hypo- and hyperthyroidism relative to racial status in goitrous subjects. Normally, the prevalence of hypothyroidism (2- 15%) is usually much higher in comparison with hyperthyroidism in the general population (Baral *et al*., 2002).

2.7 A prevalence of thyroid dysfunction in Kathmandu University Hospital, Nepal

Thyroid dysfunction is one of the most commonly encountered endocrine abnormalities. The screening of thyroid dysfunction is recommended in Nepal with its high risk population.

Many factors are responsible for exacerbating the thyroid dysfunction in the context of Nepal. Therefore, this study was designed to assess the prevalence of thyroid dysfunction in Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH) in 2010. In this hospital based retro-spective study, 825 subjects (resident of Kavre) that were subjected to thyroid function test panel (free triiodothyronine, free thyroxine and thyroid stimulating hormone) were enrolled and the thyroid dysfunction was stratified as hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism with reference to hormonal levels. Among 825 subjects, the prevalence of thyroid dysfunction was 25%. Females had more thyroid dysfunction than males. Hypothyroidism (8%) and subclinical hypothyroidism (8%) had higher prevalence compared to subclinical hyperthyroidism (6%) and hyperthyroidism (3%). Higher prevalence of thyroid dysfunction was observed in subjects with age above 30 years. In conclusion, this study revealed the higher prevalence of abnormal thyroid function and concurs with previous reports in other populations. Hypothyroidism and subclinical hypothyroidism are preponderant followed by subclinical hyperthyroidism. Females and advanced aged people are more vulnerable to thyroid dysfunction in the population. Since, it was a hospital-based study; the prevalence of thyroid dysfunction may not be applicable to the general population**.** (Madhurkar *et al,* 2010)

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Significance of the study

Thyroid disorders are very common, affecting 750 million people worldwide by recent World Health Organization (WHO) estimates, being possibly even more prevalent than diabetes. The overall prevalence of thyroid dysfunction has increased from 2.3% to 3.8% (1994-2001). The prevalence of ever having had hyperthyroidism increased from 0.86% to 1.26% in females and 0.17% to 0.24% in males. Many groups, including primary care physicians and specialists, nurses, physician assistants, health educators, medical clinics, professional medical societies, and public health personnel, provide care and assistance to those with thyroid diseases (Hossein, 2014).

Thyroid disorders typically occur when this gland releases too many or too few hormones. An overactive or underactive thyroid can lead to a wide range of health problems. A number of risk factors have been associated with thyroid disorder. Hyperthyroidism is a thyroid disorder that occurs when the thyroid gland is overactive. It can cause several problems including irritability and anxiety, menstrual irregularities, vision problem, muscle weakness, infertility and increased sweating (Leese *et al*., 2007).

Both thyroid hormones (T4 and T3) are related to heart disease because they affect heart rate and the amount of blood pumped by heart. Hypothyroidism also can lead to increased levels of LDL, total cholesterol, triglycerides, and other fats related to heart disease (Hormone.org, 2014).

The study will help to provide a recent update and to discuss about the current situation of thyroid cancer in Bangladesh. Identifying the high risk group for thyroid cancer could potentially allow preventive measure before the development of thyroid cancer. Another purpose was to raise awareness among the people about thyroid cancer so as to early detection of the thyroid disorder which helps to decrease associated complication with thyroid cancer.

Aims of the Study

The aim and objectives of the study were

1. To know the prevalence of thyroid cancer among the selected population of Bangladesh
2. To identify the vulnerability of thyroid disorder between men and women
3. To know the possible medication used to treat thyroid disorder in Bangladesh

Methodology

3.1 Types of the study

It was a Retrospective study

3.2 Study population

In this study, Total sample size was 500. Data was collected by visiting different institutes directly. The study was conducted in different Nuclear Medicine Center in Dhaka city. A total 2 center (National Institute of Nuclear Medicine and Allied Sciences (BSMMU) and Institute of Nuclear Medicine and Allied Science (Dhaka Medical College) were randomly selected for the data collection.

Institute name	Address
National Institute of Nuclear Medicine and Allied Sciences	BSMMU
Institute of Nuclear Medicine and Allied Sciences	Dhaka Medical College

3.3 Inclusion criteria

Patient having thyroid disorder

3.4 Study period

The duration of the study was about six months that started from April to September 2015.

3.5 Data analysis

Data were registered using Microsoft Excel data entry. Control of data entry was secured through both programme appliances and manually. The prevalence rates of thyroid disorder and other aspects were analyzed by simple percentage.

Results

4.1 Male and female distribution: (n=500)

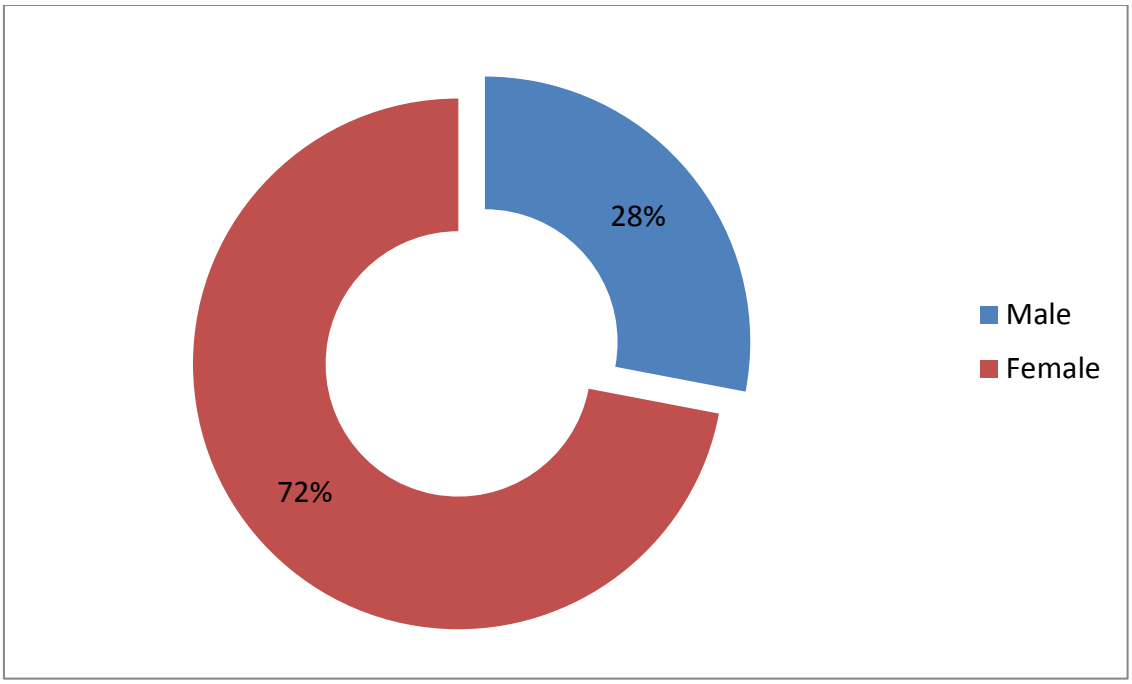

Figure 4.1: Prevalence of Male and Female distribution

The above figure shows that prevalence of thyroid disorder in male and female. Among 500 patients we see that about 72% patients were female and rest of were male.

4.2 Age Distribution: (n=500)

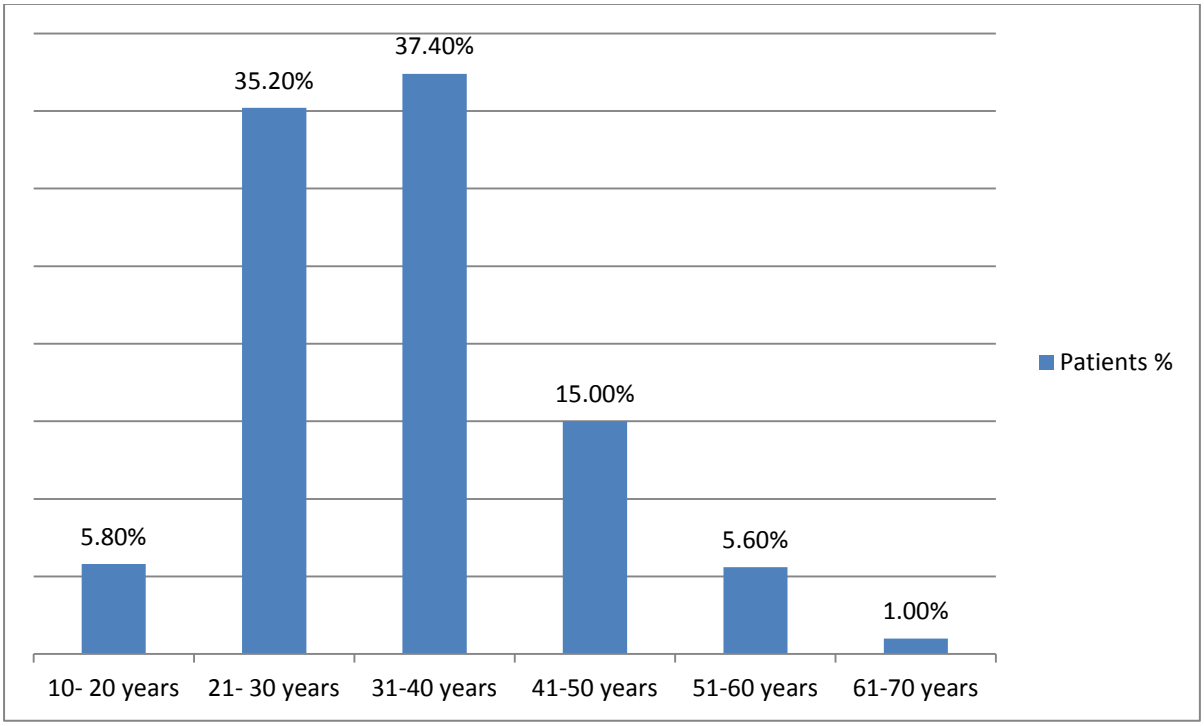

Figure 4.2: Age distribution

In this study out of 500 patients, the highest percentages of patients were in age group of 31-40 years (37.8%). The least amount (1.00%) was from 61-70 years.

4.3 TSH level (mU/L) before Radio Iodine: (n=500)

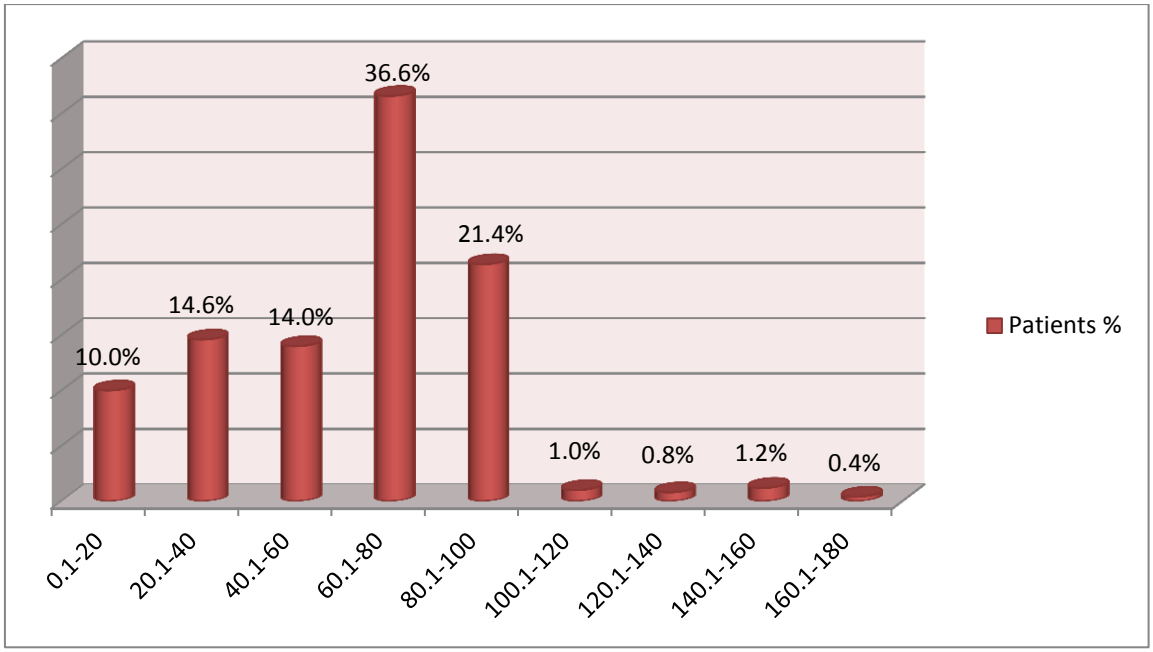

Figure 4.3: TSH level (mU/L) before Radio Iodine

From the above study we can see that the TSH level of patients before treatment with Radio Iodine. Most of the patients had TSH level (36.6%) between 60.1-80 mU/L.

4.4 TSH level (mU/L) after Radio Iodine (3 months): (n=500)

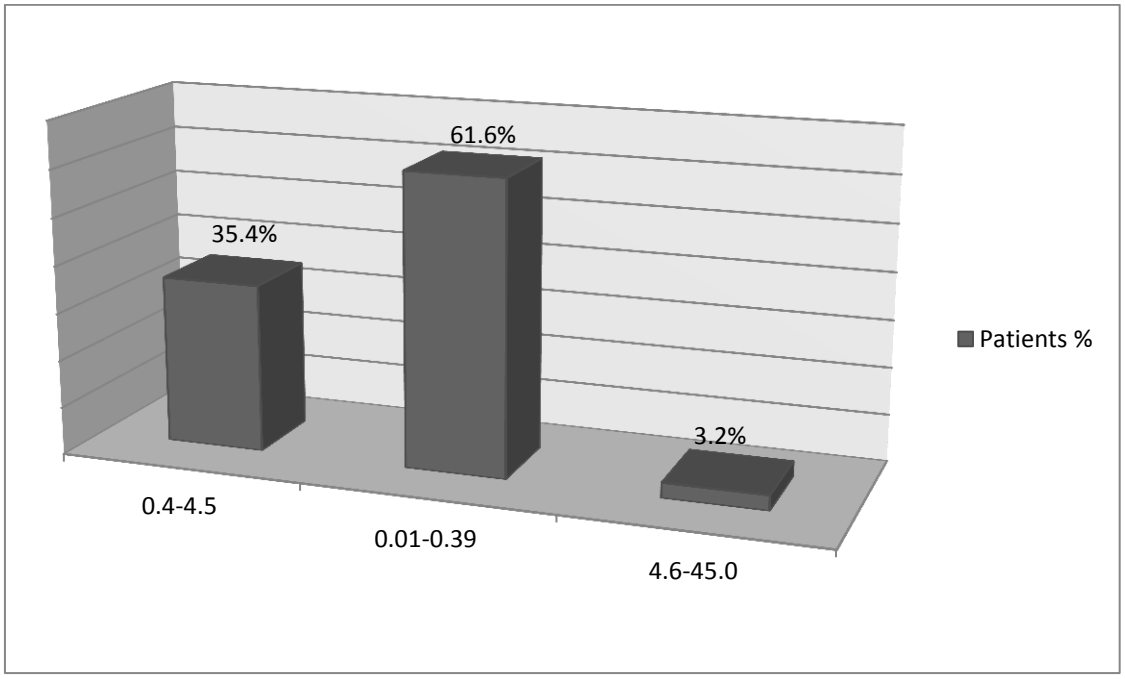

Figure 4.4 TSH level (mU/L) after Radio Iodine (3 months)

In this study we see that TSH level decrease from higher level to lower level after 3 month of Radio Iodine treatment. Most of the patients (97.3%) had TSH level between 0.01-4.5 mU/L.

4.5 fT3 and fT4 level: (n=500)

Thyroid hormones	Euthyroid (mean)	Patients hormone level (mean)
fT3 pmol/L	5.65	9.01
fT4 ng/dl	1.3	3.89

Table 4.1: Comparison of fT3 and fT4 level between Euthyroid and Hyperthyroid

In this study we see that fT3 and fT4 level was increased among the patients in comparison with euthyroid level. Both hormones level were elevated.

4.6 Triglyceride level: (n=500)

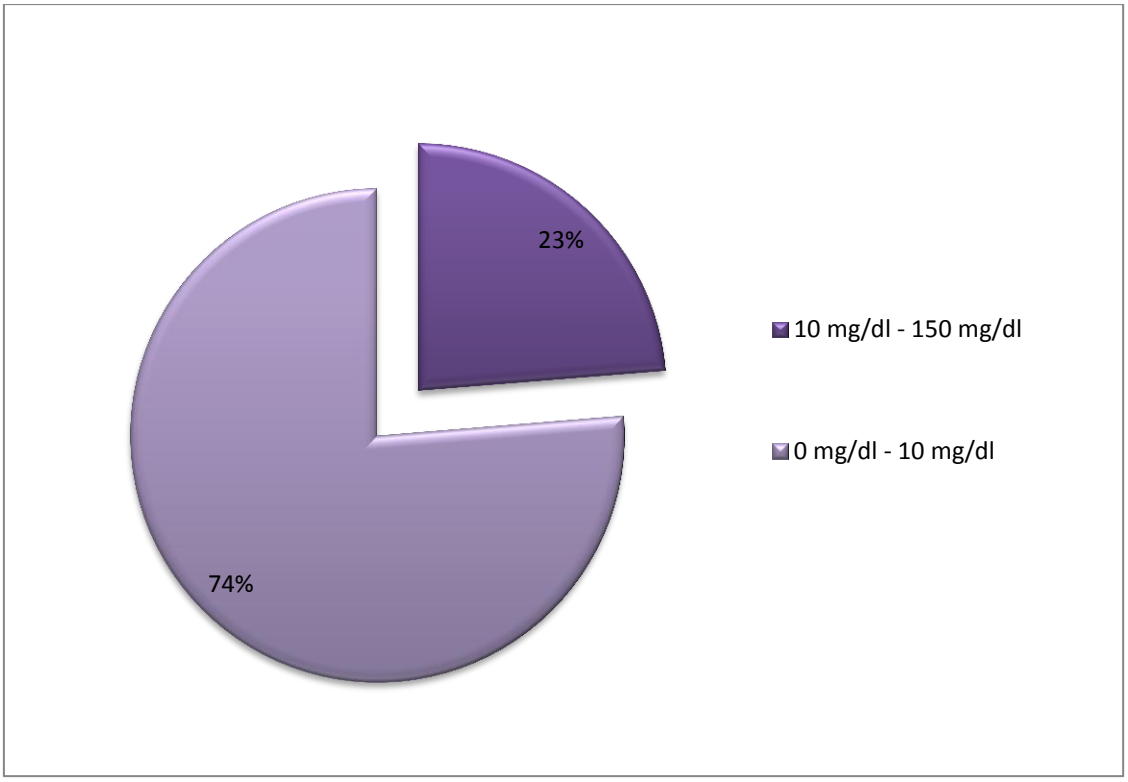

Figure 4.5: Triglyceride level among patients

From the study we see that the triglyceride level before treatment. Here about 74% patients had low triglyceride level before treatment.

4.7 Thyroglobulin level after Radio Iodine/ Thyroidectomy

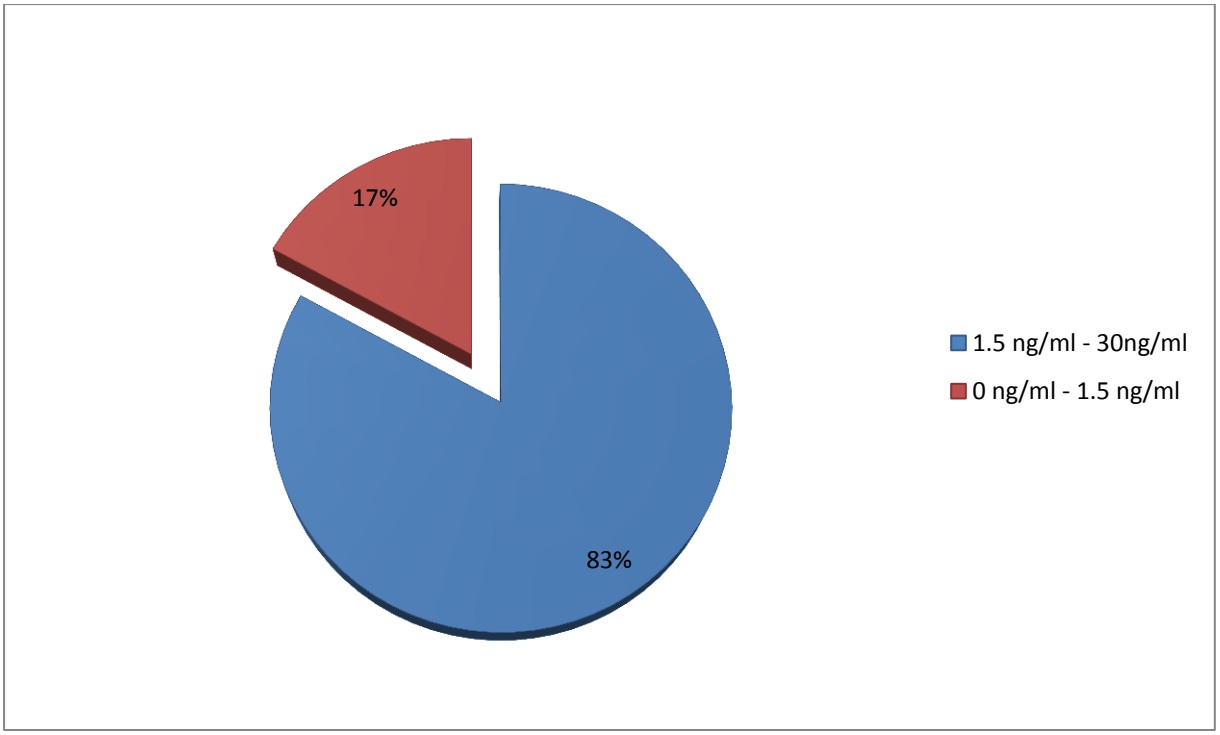

Figure 4.6: Thyroglobulin level after Radio Iodine

Thyroglobulin level is also a marker of the measurement of Tg in a blood sample which used to check whether there was any tumor left behind. From this study we see that about 83% patients had normal thyroglubin level (1.5-30 ng/dl) after treatment.

4.8 Calcium level (before Radio Iodine treatment): (n=500)

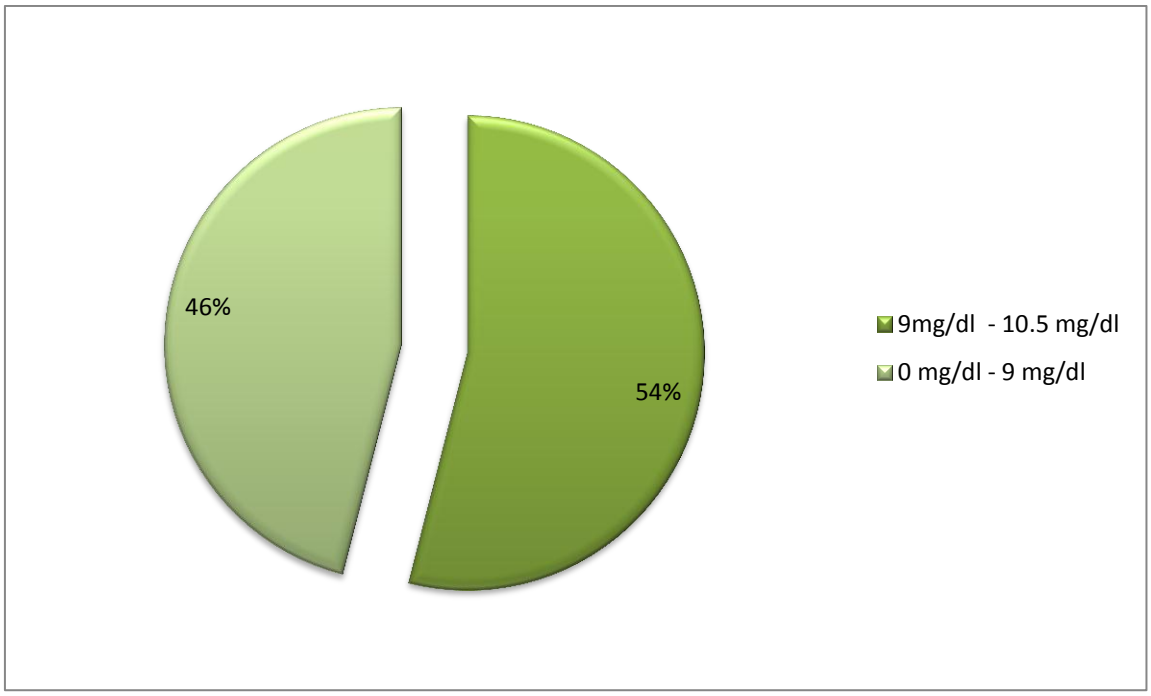

Figure 4.7: Calcium level (before Radio Iodine treatment)

From this study we can see that among 500 patients about 46% had calcium level out of normal range (9-10.5 mg/dl)

4.9 Calcium level (after Radio Iodine treatment: (n=500)

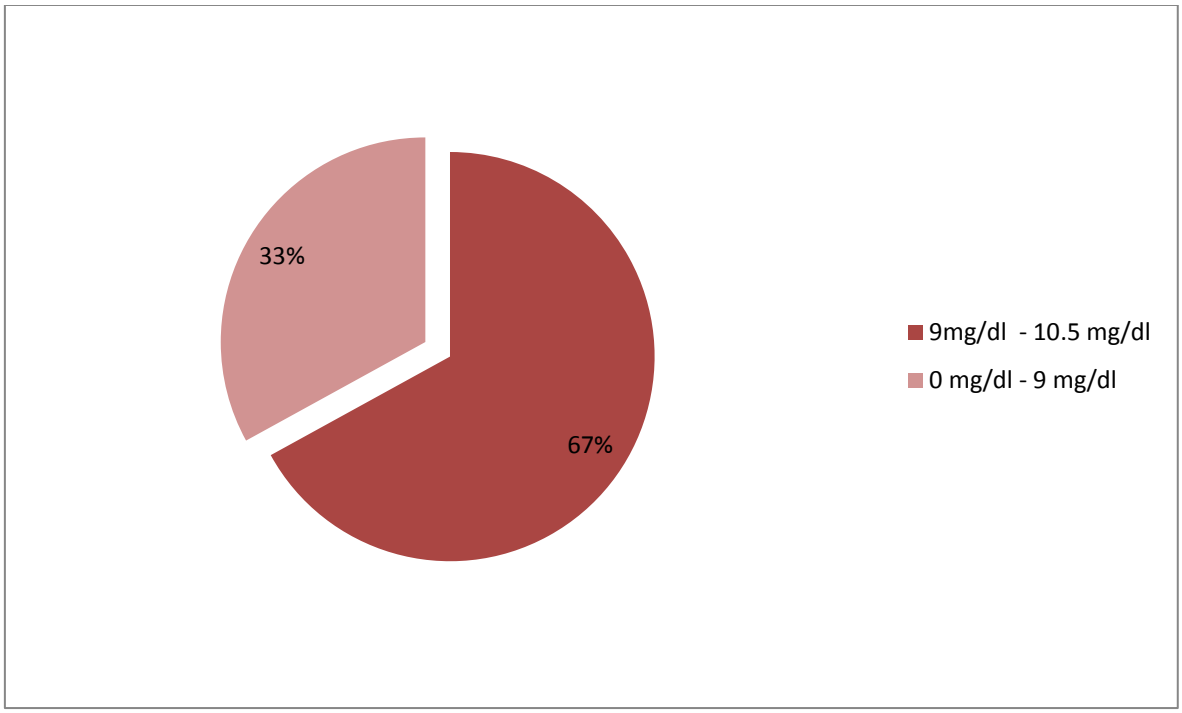

Figure 4.8: Calcium level (after Radio Iodine treatment)

In the study we see that about 67% patients had calcium level within normal range (9-10.5 mg/dl) after Radio Iodine treatment.

4.10 Medication of Thyroid disorder: (n=500)

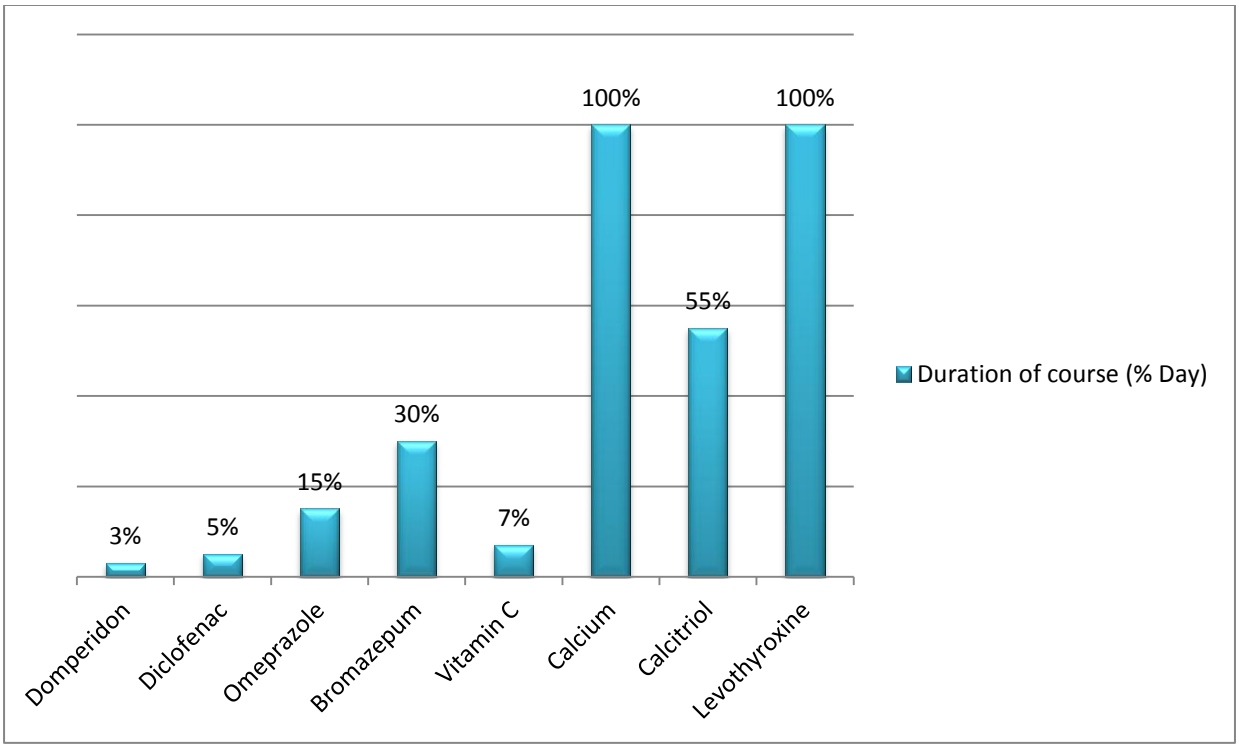

Figure 4.9: Medication of Thyroid disorder

The study found that all of the patients took Levothyroxine and Calcium (100%) for the treatment of thyroid disorder. These drugs were used by the patients' rest of their lives. They also took Domperidone, Diclofenac, Omeprazole, Bromazepum initially after treatment with Radio Iodine.

4.11 Patients' receiving Radio Iodine (mci): (n=500)

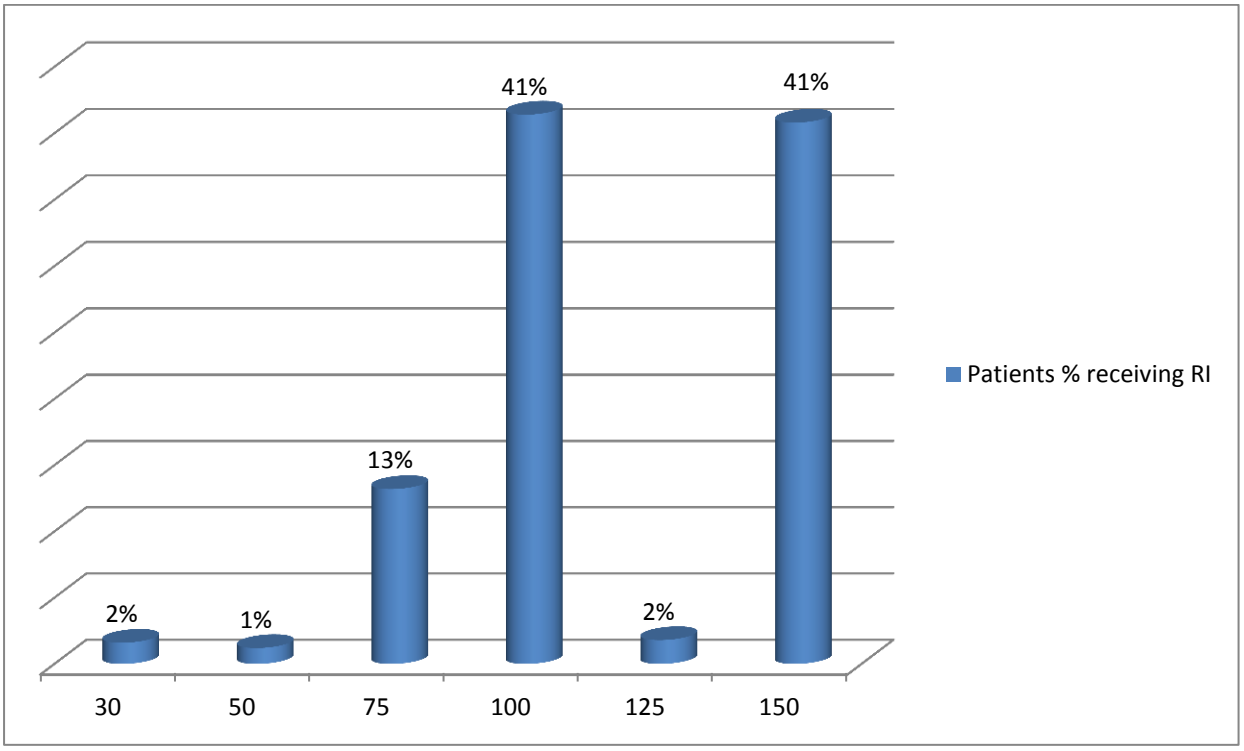

Figure 4.10: Patients' receiving Radio Iodine (mci)

From the study se see that Mostly used Radio Iodine doses were 100 mci and 150 mci. Both are used 41%.

4.12 Comparison of thyroid hormones level in male and female: (n=500)

Table 4.2: Comparison of thyroid hormones level in male and female

Thyroid hormone	Male (mean)	Female (mean)
TSH (mU/L)	66.67	62.03
fT3	8.76	9.06
fT4	3.92	3.88

From the study we see that TSH and fT3 level was higher in male than female. But women had high fT4 level.

Discussion

The thyroid is an organ that is considered part of the endocrine, or hormone, system. It is located in the neck below the Adam's apple. The thyroid's main purpose is to produce thyroid hormones. These hormones then travel through the bloodstream to all the other tissues and organs to help control metabolism in adults and growth, development, and metabolism in children (Lee, 2015). Thyroid cancer is the 16th most common cancer worldwide, with around 298,000 new cases diagnosed in 2012 (2% of the total). Thyroid cancer incidence rates are highest in Northern America and lowest in Western Africa, but this partly reflects varying data quality worldwide (Bray *et al*., 2012). Worldwide, it is estimated that there were more than 862,000 men and women still alive in 2008, up to five years after being diagnosed with thyroid cancer (Bray *et al*., 2012).

The present study was carried out on thyroid patients to see the prevalence of thyroid disorder in male and women. Out of 500 thyroid patients 72% were female and 28% were male. The American Thyroid Association (ATA) is the world's leading professional association of medical specialists dedicated to education and research to improve thyroid disease prevention, diagnosis and treatment; improving thyroid patient care; and educating the public about thyroid health and diseases. According to them Women are five to eight times more likely than men to have thyroid problems. According to our study it is clearly observed that women are more vulnerable to thyroid disease than men.

The present study found that most of the patients having thyroid disorder are in age between 20-40 years. More than 65% of people lies in between the above mentioned age range. It shows that most of people of reproductive age are suffering from the thyroid disorder. This is an alarming situation for us.

This study also shows that most of the patients have the elevated TSH level before giving the radio iodine treatment. More than 90% patients have elevated TSH level. Around 58% patients having TSH level in between 60-100 mU/L. After 3 months of treatment with Radio Iodine TSH level drastically fall down to 0.01-4.5 mU/L. The normal TSH level is 0.4-4.5 mU/L, around 35.4% patients obtained the normal TSH level after 3 months of Radio Iodine treatment.

Usually patients receive a T4 dose large enough to suppress their blood level of thyroid stimulating hormone (TSH) below the normal TSH range. This is called TSH suppression.

The ATA and ETA guidelines suggest TSH suppression when a patient has active tumor or has a very aggressive tumor that has been treated with surgery and radioactive iodine (RI 131). TSH suppression was defined as a median level of 0.4 mU/L or less. Around 62% patients have received TSH suppression therapy after treatment with Radio Iodine because after treatment for well-differentiated thyroid cancer, TSH is often suppressed because it stimulates thyroid cell proliferation (Baunfire.com, 2015 & Fiore, 2013).

The study also shows that patients had elevated fT3 and fT4 level in comparison with euthyroid level. Here patients have 9.01 pmol/l (mean) ft3 level and 3.89 ng/dl (mean) fT4 level which is higher than normal thyroid hormone level.

Thyroglobulin (Tg) Measurements after Surgery, Changes in the Tg level over time (three months or yearly intervals) are more important because of the measurement of the protein Thyroglobulin (abbreviated Tg) in blood, is an important laboratory test for checking whether a patient still has some thyroid present. This means that when a patient has had their thyroid completely removed, the measurement of Tg in a blood sample can be used to check whether there is any tumor left behind. After surgery Tg can be used as a sensitive tumor marker test (SpencerBaunfire.com, 2006). According to study the Thyroglobulin level is normal in 83% of patients after Radio Iodine treatment or Surgery.

Thyroid disorder is a common cause for low level of triglyceride level in patients. The National Cholesterol Education Program sets guidelines normal triglycerides are less than 150 milligrams per deciliter (mg/dL). Having low triglycerides is quite an uncommon health condition and denotes extremely low triglyceride level (less than 10 mg/dL) (WebMD, 2015). The present study shows that 74% patients have low level of triglyceride (less than 10mg/dL).

The main cause of low calcium levels is having the parathyroid glands in patient's neck removal. This may be necessary for some types of cancer in the neck area. Or it can occur if the parathyroid glands are damaged during thyroid gland surgery. This affects up to 5% of people after thyroid surgery. The parathyroid glands help to keep a steady level of calcium in the blood (Anon, 2015). In this study we have found that 33% patients have low level of calcium level after surgery or treatment. Before treatment the percentage was around 46%.

Conclusion

A functioning thyroid is prerequisites for healthy life. The pattern of thyroid disease may vary in different parts of the world and also in different regions of the same country. Thyroid disorder is one of the major health problems in Bangladesh. The incidence rates of thyroid cancer in both women and men have been increasing in recent years. It is also alarming that most of the people of reproductive age in Bangladesh are suffering from thyroid disorder. Thyroid disorder is more common in women than men. If mother has thyroid disorder there is chance of giving birth of a mentally retarded child which is also alarming for us. Some other adverse clinical condition such as stroke and heart attack can lead to a patient having thyroid disorder. Social awareness need to raise against thyroid diseases.

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