Dedication

To my:

MOTHOR ***who taught me that the means to ends is patience***

BROTHRS ***who stood beside me and pushed me ahead;***
particularly Dr. Asim

Kid; TAMER ***who gave me a tomorrow dream***

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SUMMARY

1214 students (594 boys and 621 girls) from Shendi basic schools and 136 patients from Shendi hospitals were subjected to study the iodine deficiency disorders in Shendi area by determination of goiter incidence among schoolchildren and thyroid function test of patients.

Methods:

1- Questionnaire: Including information about sex, age, residence, school performance, prominent features of patients and children in the study sample, source of water supply and iodized salt consumption.

2- Clinical assessment: the pupils were subjected to clinical assessment to determine the presence of goiter and it is grades. The assessment was done by palpation procedure according to WHO and ICCIDD criteria.

3- Biochemical measurements: urinary iodine excretion for schoolchildren and thyroid hormones (T_4 and T_3) and TSH of patients were measured. In addition water samples were analyzed.

Results:

The distribution of goiter incidence among schoolchildren was 14.6% and 54.6% of them were female (15.8% in female and 13.3% in male). Grade 1A goiter was more prevalent (75.2%). High incidence of goiter was observed in southern shendi (23.4%) and low incidence in eastern shendi (11.3%). Iodine deficiency had high effect on the schoolchildren performance; most of goitrous cases (53.7%) were in the low level (bad degree).

Most of cases (68.6%) showed a urine iodine concentration between 10 - 30 µg/dl. 7.9% had urinary iodine excretion more than 30 µg/dl and 23.5% of children were suffering from iodine deficiency; 17% of them had mild iodine deficiency, 3.5% of pupils showed moderate iodine deficiency and 3.8 % had severe iodine deficiency according to WHO standard. The high urinary iodine excretion was in the east of Shendi (23.40 ± 30.64 µg/dl) and the low urinary iodine excretion was in the north of Shendi (13.86 ± 3.88 µg/dl).

Most patients (61.0%) had normal thyroid hormones concentration and showed euthyroid state which may result from mild thyroid hormone deficiency due to dietary iodine deficiency. Most of patients were female (86.0%) which indicated that the thyroid disorder was affecting female more than male.

Analysis of water samples from study zones showed some minerals which are goitrogenic such as fluoride, nitrate and calcium. 4.1 % of Shendi population were using iodized salt and most of them (77.5%) did not heard about it.

ملخص البحث

1214 تلميذ (593 ذكر و621 أنثى) تم اختيارهم عشوائيا من مدارس شندى بمرحلة الأساس بعد ان تم توزيع المنطقة جغرافيا الى أربعه مناطق جغرافيه (شرق و شمال و جنوب وغرب شندى) وكذلك شملت الدر اسه 136 مريض بالغدة الدرقية من مستشفيات شندى "التعليمي– المك نمر" تهدف الدر اسه لتقصى اضطرابات نقص اليود فى المدينه وذلك بمعرفة معدل حدوث الجويتر ودرجته خلال التلاميذ وقياس وظائف الغدة الدرقية للمرضى .

طريقه البحث :–

1– **استبيان:**– يتضمن معلومات عن الجنس والعمر والمنطقة الجغرافيه ومستوى تحصيل التلميذ والغذائيات التى يتناولها ومصادر مياه الشرب واستخدام الاسره للملح الميودن

2– **فحص سريري:**– تم إجراؤه على طلاب المدارس للكشف عن وجود الجويتر ودرجته.

3– **قياسات معمليه:**– يتضمن فحص معدل إخراج اليود فى البول لتلاميذ وقياسات هرمونات الغدة الدرقية والهرمون المحفزه لها .

نتائج البحث:–

أظهرت النتائج ان معدل الجويتر خلال طلاب مرحلة الأساس هو 14.6 % ، 54.6 % منهم إناث بمعدل انتشار 15.8 % خلال الإناث و13.3 % خلال الذكور كما ان درجة الجويتر 1A "اقل درجات الجويتر) هى الاكثر إنتشارا 75.2 %.أوضحت كذلك الدر اسه ان أعلى معدل حدوث للجويتر فى منطقة جنوب شندى 23.4 % واقلها فى منطقه شرق شندى 11.3 % .

الفحص المعملي للبول لأغلبية أفراد العينه 68.8 % أظهر ان لهم قيم إخراجية ليود البول تتراوح ما بين 10 – 30 ميكروجرام /دل وهو المدى الطبيعى حسب معايير منظمة الصحة العالمية. 23.5% من أطفال العينه يعانون من نقص اليود وأن 17% منهم عند مستوى نقص اليود الخفيف ، 3.5% منهم عند مستوى نقص اليود المتوسط و 3.% عند مستوى نقص اليود الحاد. كما بينت الدر اسه أن هنالك 7.9% لهم معدل إخراج لليود مرتفع أكثر من 30 ميكروجرام/دل ومعظم تلك القيم العالية محصورة فى منطقتي شرق وجنوب شندى.

منطقة شرق شندى أظهرت أعلى قيم إخراج ليود البول بمتوسط ((30.64 ± 23.40) بينما أقل قيم كانت فى منطقة شمال شندى (3.88 ± 13.86) . كما أوضحت الدراسة أن نقص اليود له تأثير واضح على معدل التحصيل لدى التلاميذ حيث أن 53.7% من الطلاب المصابين بالجويتر لهم مستوى تحصيل منخفض للغايه.

معظم المرضى 85% متوسط قياس الهرمونات الدرقية كانت عند المستوى الطبيعى مما يعكس أن الغدة الدرقية فى حالة متوازنه هرمونيا وان التضخم الناتج يعزى للنقص الخفيف فى مستوى يود الغذاء والذي تجتهد الغدة فى تعويضه بزيادة نشاطها فوق المعدل مما ينتج عنه التضخم. كذلك وجدت الدراسه أن معدل المرض الدرقي ينتشر خلال الإناث أكثر من الرجال. (86% ، 14% على التوالى)

تحليل عينات مياه من مصادر مياه الشرب فى المناطق الجغرافيه الأربعه عكست وجود بعض العناصر المعدنية التى تعيق إمتصاص اليود فى الجسم مثل الفلور والنترات. غالبية سكان شندى (77.5%) لا يستعملون الملح الميودن فى طعامهم و القليل الذين يعرفون أهميته لا يستخدمونه بانتظام، كما أن التعامل معه يخضع بدرجة كبيرة لمستوى تعليم رب الأسرة.

TABLE OF CONTENTS

CHPTER ONE

1- INTRODUCTION AND LITRETURE REVIEW

CHPTER THREE

CHAPTER FOUR

FIGURES & TABLES

1- FIGURES:

2- TABLES:

ELNEELAIN UNIVERSITY
GRADUATE COLLEGE

IODINE DEFICIENCY DISORDERS IN SHENDI CITY - NORTH OF SUDAN

A THESIS
SUBMITTED IN ACCORDANCE OF THE REQUIREMENT
OF ELNEELAIN UNIVERSITY FOR THE DEGREE OF DOCTOR OF
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1-1: Introduction

Iodine is natural element, mineral, and like carbohydrate, fats, proteins, and vitamins is an essential constituent of human diet. Iodine is also called "micronutrient" like vitamin A and iron because it is requirement in very small amount by our body.

Thyroid hormones are essential for normal growth, development and functioning of both the brain and body. Lack of iodine result in deficiency of these hormones and result in a wide spectrum of disorders, collectively called iodine deficiency disorders (IDD). The most visible and easily recognized sign of iodine deficiency disorders is goitre.

Thyroid gland disorders are common worldwide problems. Shendi province is not an exception regarding this problem, furthermore it is observed that most of the patients with thyroid disorders presented to Shendi hospitals from certain areas. This observation draw out attention and interest to conducted a study on these disorders in relation to iodine status.

Objectives of the study:

The present study was planned to:

- Determine of incidence of iodine deficiency disorder among the basic schools' children in Shendi city centre.
- Co-relation of iodine deficiency disorder and school performance of children in study area.
- Role of water supplements to iodine intake by inhabitant in study area.

- Assessment of the thyroid functions of hospital patients presenting with thyroid symptoms.

1.2: Thyroid Gland

1.2.1: Anatomical consideration:

The thyroid gland was discovered by Wharton in 1656. In 1874, Gull described thyroid hypofunction in man. In 1895, Magnus Levy reported increased basal metabolic rate (BMR) in patients with hyperthyroidism (Satoskar, *et al*, 1997). The thyroid gland develops from a midline thickening of the pharyngeal floor and paired caudal extension of the fourth pharyngobronchial pouches, by 50 days, lateral, medial anlagen fuse, and the buccal stalk ruptures. Then the gland immigrates caudally to its definitive location in the anterior neck, the gland become mature by 17 weeks of gestation (Fisher, 1992).

The adult thyroid is composed of two lateral lobes joined across the midline by an isthmus; it is firm, reddish brown and smooth. Histologically, the thyroid gland is composed of follicles, which are lined by cuboidal epithelial cells and contain colloid; a pink-staining proteinaceous material composed mainly of thyroglobulin and stored thyroid hormones (Danish, 2005). The normal gland weights 20 – 25g. the functioning unit is lobule supplied by single arteriole and consisting of 20 – 40 follicles (Mann, *et al*, 1995).

The gland is highly vascularized, and the gland has one of the highest rates of blood flow per gram of tissue of any organ in the body. When the gland is inactive, the colloid is abundant, the follicles are large and the cells lining them are flat. When the gland is active the follicles are small, the cells are cuboidal or columnar, and the edge of the colloid

is scalloped, forming many small "reabsorption lacunae" (Ganong, 1995).

The thyroid gland produces three hormones, thyroxine (T_4), triiodothyronine (T_3) and calcitonin. Kendall achieved the isolation and Harrington and Barger determined crystallization of the thyroxine in 1915 and the chemical structure in 1926. Triiodothyronine was detected, isolated and synthesized by Gross and Pitt-Rivers in 1952 (Satoskar, *et al*, 1997).

Calcitonin is polypeptide; it is secreted by special listed epithelial cells (C cell) which lie between the thyroid acini. Calcitonin lowers the concentration of calcium in the blood by causing increased deposition of bone crystal. T_3 & T_4 are essential for normal physical and mental development and the metabolism of protein, fat and carbohydrate (Anderson,1982)

The thyroid cells have 3 functions: they collect and transport iodine; they synthesize thyroglobulin and secrete it into the colloid; and they remove the thyroid hormones from the thyroglobulin and secrete them into the circulation (Ganong, 1995).

1.2.2: Thyroglobulin:

Thyroglobulin is a large, iodinated and glycosylated protein. It is synthesized and glycosylated in the rough endoplasmic reticulum of the thyroid cells, and then incorporated into the exocytosis vesicles that fuse with the apical cell membrane (Dunn, 2000). Thyroglobulin is secreted into the colloid by exocytosis of granules (Ganong,1995).

Thyroglobulin is the precursor of T_4 and T_3. Carbohydrates account for about 8-10% of the weight of thyroglobulin and iodide for about 0.2-1 %. About 70% of the iodide in the thyroglobulin exists in an

inactive precursor, monoiodotyrosine (MIT) and diiodotyrosine (DIT), while 30% is an iodothyronyl T_4 and T_3 (Murry,*et al*,1993).

About 70% of the iodide in the thyroglobulin exists in an inactive precursor, monoiodotyrosine (MIT) and diiodotyrosine (DIT), while 30% is an iodothyronyl T_4 and T_3. About 100 µg of thyroglobulin is released from the thyroid gland per day (Van Herle.1979).

When iodine supplies are sufficient, the $T_{4:}$ T_3 ratio is about 7:1. In iodine deficiency, this ratio decreases, as does the DIT:MIT ratio (Murry,etal,1993). The normal serum thyroglobulin concentration in human is about 6 ng/ml, this level is increased in hyperthyroidism and some forms of thyroid cancer (Ganong, 1995).

1-2-3: Iodine metabolism

The relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U shaped with an increase in risk from both low and high iodine intakes (Laurberg, *et al*, 2001). Although iodine is found in many foods, it is not universally present in all soils in adequate amounts. The soils of many island areas on all continents are iodine deficient, and plants and animals grown there are correspondingly deficient. Populations living in those areas without outside food sources are most at risk for iodine deficiency diseases (Epidemiology, 1992). Areas where iodine supplies are inadequate see high rates not only of goitre but also of birth defects and retardation of both mental and physical development (Lamberg, 1993). Both iodine deficiency and inability to use iodine properly make the thyroid gland unable to produce thyroid hormone (Ingenbleek, 1979).

1-2-3-1: Sources of iodine:

Iodine is found naturally in foods from the ocean, such as fish and seafood, kelp, and sea vegetables, and in plant and animal products produced in areas where soil and water contain sufficient iodine (Lamberg, 1993). Eggs and milk are good dietary sources of iodide (Satoskar, *et al*, 1997). Despite coming from the ocean, sea salt is not a good source of iodine. Foods that contain iodine include onions, cheese, yoghurt, radishes and watercress. Some vegetables also contain iodine, but only if they are grown in iodine rich soil. Iodized salt is perhaps the most common source of iodine (Eastman, 1999).

1-2-3-2: Functions of iodine:-

(i) Required for manufacture of thyroxine and therefore control of metabolic rate.

(ii) Essential for normal development of the fetal nervous system.

(iii) May protect against the effect of radioactivity.

(iv) Can regulate the effect of oestrogen on breast tissue.

(v) A required component of healthy connective tissue (NHIC, 2008).

1-2-3-3: Iodine production:

Today, iodine production is conducted in areas where iodine concentration is high in brines from natural gas fields and oil fields, and in Chilean caliches deposits. About 1/3rd of the total iodine production in the world comes from Japan. Together, Chile and Japan produce nearly 90% of the world's iodine (ICCIDD, 2008).

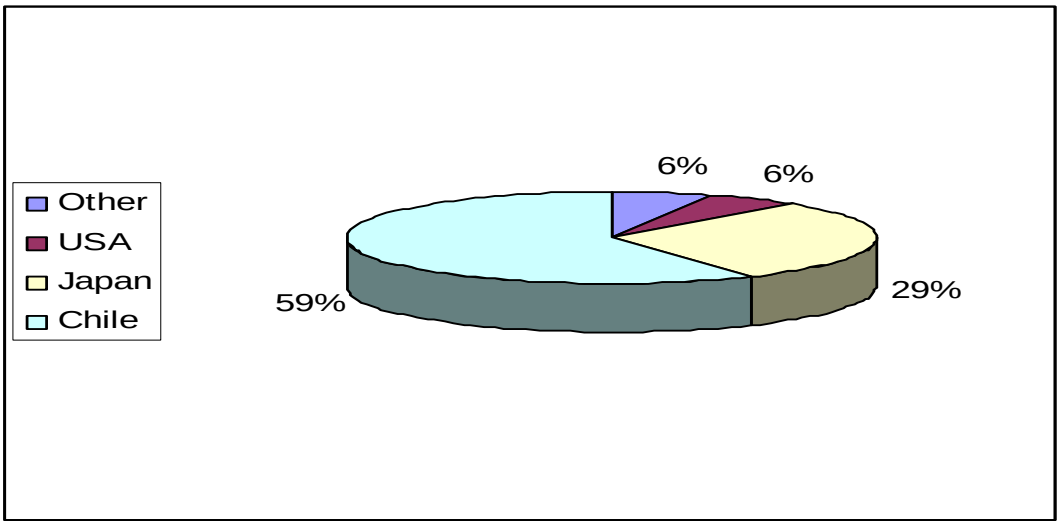


Figure (1-1): World Iodine Production (ICCIDD,2008)

1-2-3-4: Recommended iodine intake

WHO, UNICEF, and ICCIDD recommend that the daily intake of iodine should be as follows (WHO, 2001).

(i) 90 µg for preschool children (0 to 59 months).

(ii) 120 µg for schoolchildren (6 to 12 years).

(iii) 150 µg for adults (above 12 years).

(iv) 200 µg for pregnant and lactating women.

1-2-3-5: Iodine absorption:

Ingested iodide is absorbed readily in the gastrointestinal tract. Iodide is actively absorbed from the bloodstream by a process called 'iodine trapping' and concentrated in the thyroid follicles (Kierkegaard and Faber, 1998) and any excess amount is filtered by the kidneys and excreted in urine (Mertz,1986). The normal plasma iodide level is about 0.3 µg /dl and iodide is distributed in a space of approximately 25L (35% of body weight). 20% of total amount of iodide enters the thyroid whereas 80% is excreted in the urine (Ganong, 199).

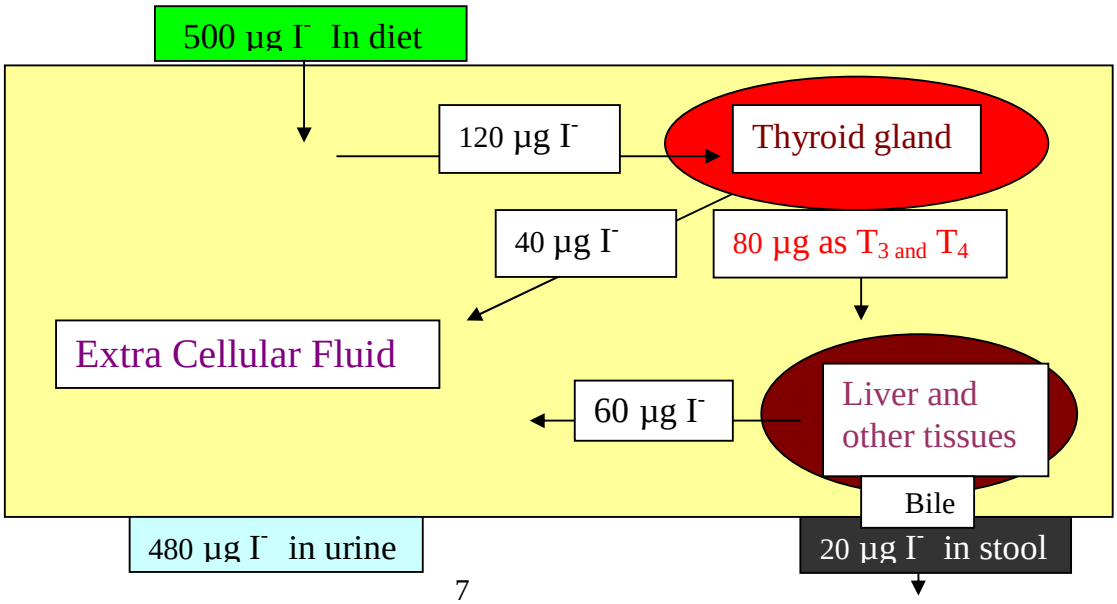


Figure (1-2): Iodine metabolism in the body.

1-2-3-6: Factors affecting iodine levels (Goitrogens):-

Goitrogens are foods, which suppress thyroid function by interfering with the thyroidal uptake of iodine. Goitrogens interfere with hormonal synthesis and the blood level of the hormone falls, increased amount of the TSH is secreted by the anterior pituitary, this in turn, stimulates the thyroid which shows hypertrophy, hyperplasia and increase in vascularity (Satoskar, *et al*, 1997).

***(i)Vegetables*:-**

A number of commonly eaten foods have been shown to interfere with the use of iodine by the thyroid, thus reducing production of thyroid hormone and causing goitre. These foods, known as goitrogens, such as vegetables in the *Brassicaceae* family particularly rutabagas, cabbage, and turnips, contain progoitrin and substance that convert this compound into goitrin, an active antithyroid agent. The progoitrin activator in vegetables is heat-labile, but because there are activators in the intestine (presumably of bacterial origin). Goitrin is formed even if the vegetables are cooked and it their intake on normal mixed diet is usually not great enough to be harmful, but in vegetarians and food faddists cabbage goitre do occur (Ganong,1995).

Other goitrogenic vegetables include mustard (Stoewsand, 1995), millet (Sartelet, *et al*, 1996), soybeans (Divi, *et al*, 1997), pine nuts (Gaitan, 1990), . People who consume adequate iodine can safely eat these foods in moderate amounts. A combination of low iodine intake

and high intake of goitrogenic foods increases the likelihood of goitre (Gaitan,1988&1990).

Soy protein in some way interferes with the normal reabsorption of organic iodine and does not affect the absorption of inorganic iodine. The increased fecal loss of iodine produces a drain on the iodine supply and can lead to a hypothyroid condition if additional iodine is not supplied in the diet (Van Middlesworth, 1957). Additional evidence that soybean meal interferes with organic iodine absorption was the inability of a patient to respond to thyroxine therapy (Pinchera, *et al*, 1965).

Goitrogens are also present in peanuts and tea. However, the goitrogens present in such foods can be largely inactivated by cooking .Tea then become the exception and drinking large amounts of tea will definitely affect iodine absorption and usage (NHIC, 2005).

Animal fats and vegetable oils increase the iodine requirement. It was further stated that vegetable oils are more goitrogenic than animal fats (Kalkus,1920). Other naturally occurring goitrogens can aggravate or stimulate iodine deficiency, and these include such foods as cassava, maize, bamboo shoots, sweet potatoes, and lima beans. Iodine deficiency and/or these goitrogens interfere with the production of thyroid hormone, thus causing an increase in TSH, an increased size of the thyroid gland (goitre), and hypothyroidism (Volpe, 1998).

As general, two categories of foods that have been associated with disrupted thyroid hormone production in humans: soybean-related foods and cruciferous vegetables. Soybean-related foods included in the category of soybean-related foods are soybeans themselves as well as soy extracts, and foods made from soy, including tofu and tempeh.

While soy foods share many common ingredients, it is the isoflavones in soy that have been associated with decreased thyroid hormone output.

Isoflavones are naturally-occurring substances that belong to the flavonoid family of nutrients. Flavonoids, found in virtually all plants, are pigments that give plants their amazing array of colors. Isoflavones like genistein appear to reduce thyroid hormone output by blocking activity of an enzyme called thyroid peroxidase. This enzyme is responsible for adding iodine onto the thyroid hormones (Toda, *et al*, 1999).

A second category of foods associated with disrupted thyroid hormone production is the cruciferous food family. Foods belonging to this family are called "crucifers," and include broccoli, cauliflower, Brussels sprouts, cabbage, mustard, rutabagas, kohlrabi, and turnips. Isothiocyanates are the category of substances in crucifers that have been associated with decreased thyroid function. Like the isoflavones, isothiocyanates appear to reduce thyroid function by blocking thyroid peroxidase, and also by disrupting messages that are sent across the membranes of thyroid cells (Fowke, *et al,* 2001).

(ii) Minerals:-

A number of minerals, which restrict iodine uptake by the thyroid gland, are goitrogenics such as;

***Fluoride*:** Fluorides are cumulative and build up steadily with ingestion of fluoride from all sources, which include not just water but also the air we breathe and the food we eat. The use of fluoride toothpaste in dental hygiene and the coating of teeth are further sources of substantial levels of fluoride intake (Goldemberg, 1921).

The 1970s, European doctors used fluoride as a thyroid-suppressing medication for patients with hyperthyroidism (over-active thyroid). Fluoride was utilized because it was found to be effective at reducing the activity of the thyroid gland even at doses as low as 2 mg/day (National Research Council, 2006).

The increasing use of fluoride for prevention of dental caries poses the problem as to whether this halogen has antagonistic properties towards iodine, whereby it could hamper the success of iodine prophylaxis of endemic goitre (Burgi, *et al*, 1984). Fluoride damage thyroid system in 4 levels:

(i) The enzyme manufacture of thyroid hormones within the thyroid gland itself. The process by which iodine is attached to the amino acid tyrosine and converted to the two significant thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) is slowed.

(ii) The stimulation of certain G proteins (whose function is to govern uptake of substances into body cells) from the toxic effect of fluoride, has the effect of switching off the uptake into the cell of the active thyroid hormone.

(iii) The thyroid control mechanism is compromised. The thyroid stimulating hormone output from the pituitary gland is inhibited by fluoride, thus reducing thyroid output of thyroid hormones.

(iv) Fluoride competes for the receptor sites on the thyroid gland, which respond to the thyroid-stimulating hormone; so that less of this hormone reaches the thyroid gland and so less thyroid hormone are manufactured (Goldemberg, 1921).

Fluoride exposure in humans is associated with elevated TSH concentrations, increased goitre prevalence, and altered T_4 and T_3

concentrations; similar effects on $T_4$and T_3 are reported in experimental animals. Fluoride effect on thyroid function, for instance, might depend on whether iodine intake is low, adequate, or high. In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate (National Research Council, 2006).

Nitrate: is a wide spread contaminant of ground and surface water. The source of nitrate in the ground water may be from run off or seepage from fertilized soil, municipal or industrial wastewater, landfills septic system, urban drainage or decaying plants. Human and animal systems are affected severely on nitrate exposure (Mukhopadhya, *et al,* 2005). Nitrates are readily absorbed and their excretion is similar to that of halogen ions. Several monovalent anions, including nitrate, when injected into animals interfere with the uptake of iodine by the thyroid. Dietary levels of 0.5%,1.0% and 2.5% also reduce the rate of iodine uptake by the thyroid (Genva,1974).

Nitrate is primarily absorbed from the upper part of the human digestive tract (Batholomew, *et al,* 1984). In the blood, nitrates compete with the transport of iodide in the thyroid. With normal supply of iodide, outweighing of this transportation mechanism adjusts the competition of nitrate. However if the offer of iodide is scarce and the nitrate pollution is high, the thyroid seeks to adjust the lack of iodide (which is intensified artificially by nitrate) by enlargement and new formation of thyroxin forming cells. If this is not successful, iodine lack can cause damages (Office of Drinking Water, 1990).

Experimental results indicate that 0.31 and 0.92 percent of dietary nitrate, when consumed by rats and sheep respectively, can affect the

normal iodine metabolism of the thyroid gland. The dietary level of iodine appears to be highly important when nitrate is present in the diet (Bloofield, *et al,* 1961). The toxicity of nitrate in humans, as well as in animals, depends on the conversion of nitrate to nitrite. For this reason, infants and patients with hypo- or achlorhydria and/or stomach lesions are to be considered as special risk groups (Speijens, *et al*, 1987). Poisoning in man may result from a total oral daily dose in excess of (4g) or from a single dose of more than 1g. The safe upper limit for nitrate in the drinking water of babies is probably 10-20 ppm (Geneva, 1974).

Other minerals: High levels of minerals such as calcium and magnesium, and certain bacteria in drinking water, have also been shown to be goitrogenic. Therefore, proper nutrition and a healthy water supply are crucial in the prevention and treatment of goitre (Gaur, *et al*, 1989). High calcium diets may increase the need for additional iodine (Sampson, *et al,* 1952). The goitrogenic effect of a high calcium diet is not from a lowered intestinal absorption of iodine. Since about 2% of calcium carbonate is needed to produce this goitrogenic effect, calcium probably does not play an important role in most rations (Taylor, 1954).

There are other goitrogenic factors, such as thiocyanates and thiourea. The action of these goitrogenic substances is not simply to increase the need for added iodine, but they interfere with the production of thyroxine (Ripp, 1961). Other factors, which have been related to iodine utilization or thyroid function, include manganese, amino acids, and Vitamin A (Van Koetsveld, 1964).

1-2-4: Thyroid hormones synthesis

The thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) are tyrosine-based hormone produced by the thyroid gland. An important component in the synthesis is iodine (Kirkegaard and Faber, 1998). Thyroid hormones are unique in that they require the trace element iodine for biologic activity. Thyroid hormones play a major role in regulating the metabolism of most cells, the growth and development, especially in infants and children (Editorial, 1986).

1-2-4-1: Iodide trapping:

The transport mechanism of iodide from the circulation to thyroid colloid, called trapping mechanism or iodide pumping (Ganong, 1995). This is an energy-dependent Na^+/K^+ process and is linked to the ATPase dependent Na^+/K^+ pump (Murry, *et al*, 1993).

Thyroid Stimulating Hormone (TSH) stimulates the active transport mechanism of iodide. Since the availability of iodine in the interstial environment is limited, the thyroidal follicular cells have adopted a mechanism to concentrate and conserve this important trace element. Accumulation of iodide (I^-) by the thyroid was already known to be an energy-requiring mechanism when its Na^+ dependence was recognized (Dai, *et al*, 1996).

The salivary gland, the gastric mucosa, the placenta the ciliary body of the eye, the choroid plexus, and the mammary gland also

transport iodide against a concentration gradient, but their uptake is not affected by TSH (Ganong, 1995).

A wide variety of monovalent anions with a similar ionic radius, including perchlorate (ClO_4^-), thiocyanate (SCN^-) and nitrate (NO_3^-), were found to generate similar steady-state inward currents as does I^-, suggesting that these anions are also transported by the sodium/iodide symporter (NIS) and act as iodide for its carrier and are concentrated by the thyroid gland (Vansande,*et al*,1954). The ability of perchlorate to inhibit thyroidal iodine uptake, thereby potentially inducing hypothyroidism, has been recognized many decades ago, even resulting in therapeutic applications for hyperthyroidism (Goldley and Stanbury, 1954).

1-2-4-2: Oxidation of iodide:

The thyroid gland is the only tissue that can oxidize iodide to higher valence state, an obligatory step in iodide organification and thyroid hormone biosynthesis. This step involves aheme-containing peroxides and occurs at the luminal surface of the follicular cell. A number of compounds inhibit iodide oxidation; the most important of these are thiourea drugs (Murry,*et al*,1993).

1-2-4-3: Iodination of tyrosine:

Via a reaction with the enzyme thyroperoxidase, oxidative iodide is covalently bound to tyrosine residues in the thyroglobulin molecules, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT) (Dratman and Gordon, 1996). The position 3 of the aromatic ring is iodinated first and then position 5 to form MIT and DIT respectively. This reaction, sometimes called organification, occurs within seconds in luminal thyroglobulin. Once iodination occurs, the iodine does not readily leave

the gland. Free tyrosine can be iodinated, but it is not incorporated into protein, since RNA not recognizes iodinated tyrosine (Murry, *et al*, 1993).

1-2-4-4: Coupling of iodotyrosyls:

The coupling process is not random; T_4 and T_3 are formed in regions of the molecule with unique amino acid sequences (Van Herle, *et al*, 1979). The molecules MIT and DIT undergo an oxidative condensation (coupling to form T_3 and T_4 with the elimination of alanine side chain from the outer ring). Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T_3" (Tsai and Malley, 1994).

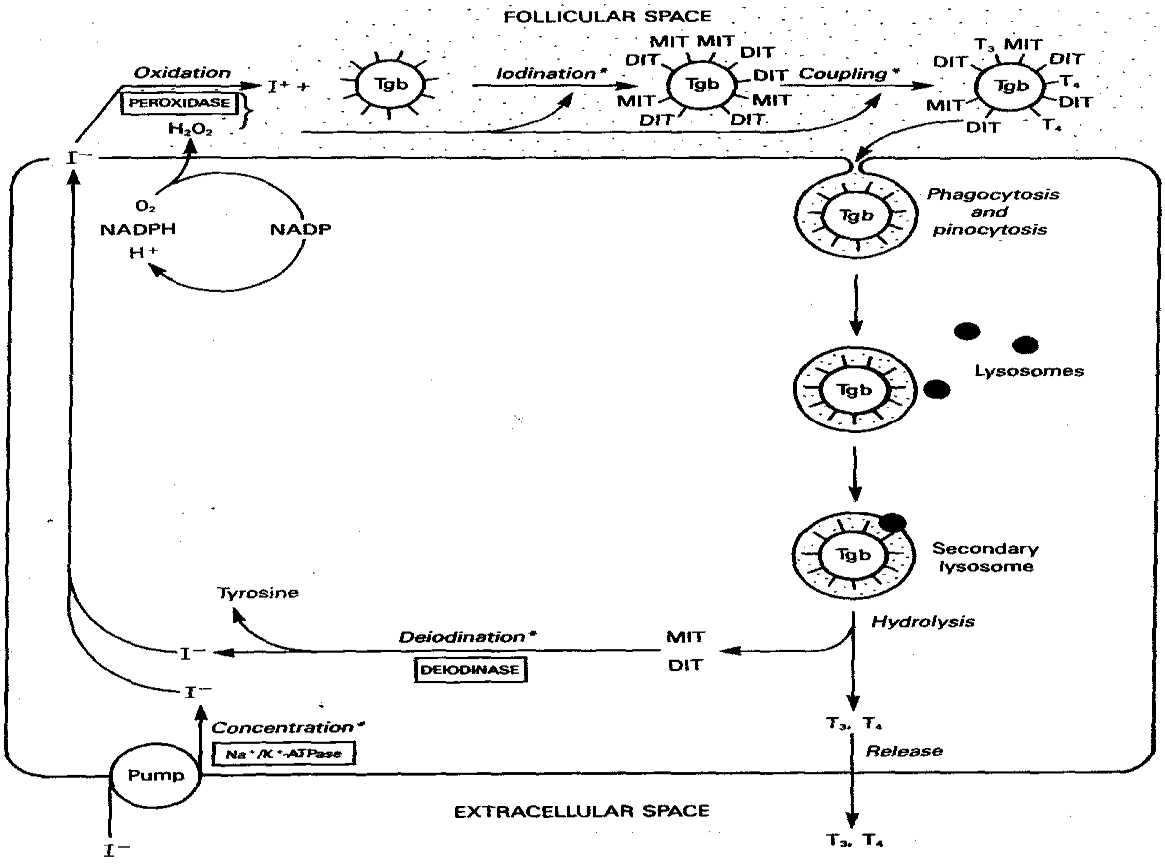


Figure (1-3): Thyroid hormones synthesis

MIT + DIT → triiodothyronine (usually referred to as T_3)

DIT + DIT → thyroxine (referred to as T4)

DIT + MIT → r-T_3 (biologically inactive)

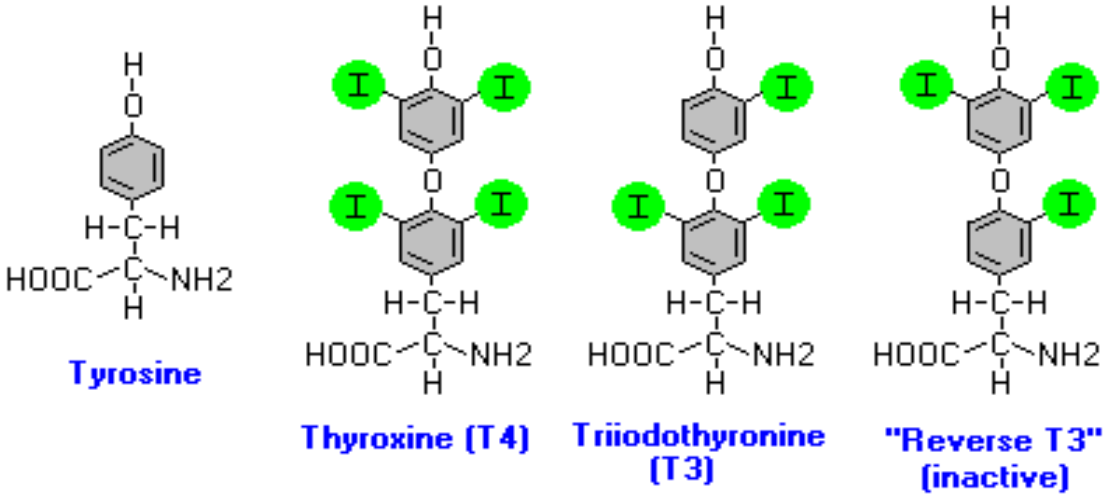


Figure (1-4): The structure of thyroid hormones.

The same thyroperoxidase catalyzes the coupling reaction by stimulating free radical formation of iodotyrosine. This hypothesis is supported by the observation that the same drugs, which inhibit iodide oxidation, also inhibit coupling (Murry, *et al*, 1993).

The mammary glands also bind iodine and diiodotyrosine is formed in mammary tissues, but T_3 and T_4 are not. Nonthyroidial tissues may form trace of T_4, but if such formation does occur, the amount is insufficient to prevent the development of the full picture of hypothyroidism after surgical thyroidectomy (Ganong, 1995).

Due to inborn errors of metabolism, one or other of these steps is sometimes deficient and this leads to the condition of dyshormonogenesis, thus failure of the iodide trapping mechanism, defective organification of iodide due to peroxidase deficiency ,secretion of abnormal iodoprotein and dehalogenase deficiency each constitutes a different form of dyshormonogenesis and result in a tendency to hypothyroidism (Anderson , 1982).

1-2-4-5: Secretion of thyroid hormones:

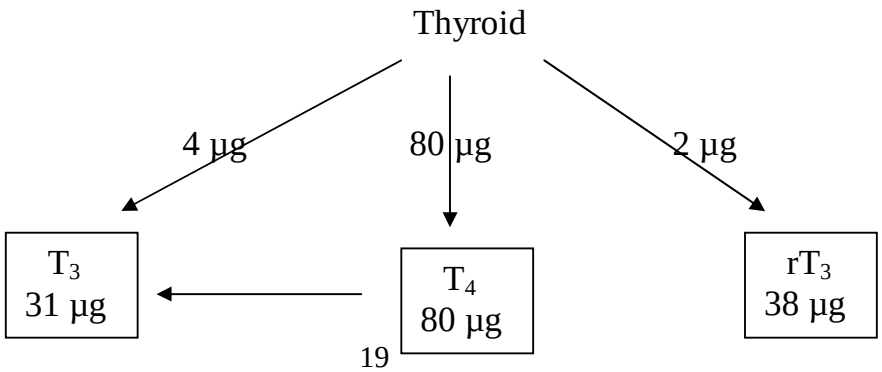
The secretion of thyroid hormones is mainly controlled by TSH. Inadequate plasma levels of T_3 and T_4 causes release of TSH from the pituitary by a feedback mechanism and this activates adenylcyclase activity of thyroid epithelium and, by increasing cAMP stimulates all the processes of thyroid hormones formation and release (Bennett and Brown, 2003).

After the stimulation of the gland by TSH (or cAMP), there is a marked increase in microvilli on the apical membrane. This microtubule-dependent process entraps thyroglobulin, and subsequent pinocytosis brings it back into the follicular cell. The phagosomes fuse with lysosomes to form phagolysosomes in which various acid proteases and peptidases hydrolyze the thyroglobulin (Ganong, 1995). Proteases digest iodinated thyroglobulin, releasing the hormones T_4 and T_3, the

biologically active agents central to metabolic regulation (Dratman and Gordon, 1996).

T_4 and T_3 are discharged from the basal cell, perhaps by a facilitated process, into the blood (Murry,*et al*,1993). Thyroglobulin hydrolysis is stimulated by TSH but is inhibited by iodide; this latter effect is occasionally exploited by using potassium iodide to treat hyperthyroidism (Ganong, 1995). When the plasma level of throid hormone exceeds the physiological requirement of the body, the production of TSH by the pituitary is suppressed and the thyroid reverts to its resting state with diminished hormone production, diminished secretion and increased storage of hormone within the eosinphilic colloid which accumulate within acini (Bennett and Brown, 2003).

In the normal human thyroid, the average distribution of iodinated compound is 23% MIT, 33% DIT, 35% T_4, 7% T_3 and only traces of rT_3 and other components are present. The human thyroid secretes about 80 µg (103nmol) of T_4, 4 µg (7nmol) of T_3 and 2 µg (3.5nmol) of rT_3 per day (Ganong, 1995). Thyroxine is supposedly a prohormone and a reservoir for the most active and main thyroid hormone T_3. T_4 is converted as required in the tissues by deiodinase. Deficiency of deiodinase can mimic an iodine deficiency. T_3 is more active than T_4 and is the final form of the hormone, though it is present in less quantity than T_4 (Dratman and Gordon, 1996).



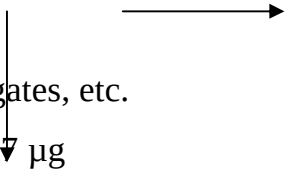


Figure (1-5). Secretion and interconvertion of thyroid hormones in normal adult human

1-2-4-6: Plasma protein:

Most of the thyroid hormone circulating in the blood is bound to transport protein. Only a very small fraction of the circulating hormone is free (unbound) and biologically active, hence measuring concentrations of free thyroid hormones is of great diagnostic value. When thyroid hormone is bound, it is not active, so the amount of free T_3/ T_4 is what is important. For this reason, measuring total thyroxine in the blood can be misleading (Kirkegaard and Faber, 1998).

One-half to two-third of T_4 and T_3 in the body is extra thyroidal, and most of this circulates in bound form, i.e., bound to two specific binding proteins thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA). The small-unbound (free) fraction is responsible for the biologic activity (2 ng/dl of T_4 and 0.3 ng/dl of T_3). The free thyroid hormone in plasma inhibits pituitary secretion of TSH by feedback mechanism. The function of protein binding appears to be the maintenance of a large pool of readily available free hormone (Murry, *et al*, 1993).

Type	Percent
Bound to thyroxine-binding globulin (TBG)	70%
Bound to thyroxine-binding prealbumin (TBPA)	10-15%

Albumine	15-20%
Unbound T_4 (free T_4)	0.03%
Unbound T_3 (free T_3)	0.3%

Table (1-1) bound and unbound forms of thyroid hormones.

The concentration of TBG is raised by oestrogens (including doses of used in oral contraception), prolonged use of neuroleptic, and in pregnancy. The concentration of TBG is lowered by adrenocortical and androgen (including anabolic steroid) therapy and by urinary protein loss in nephritic syndrome. Phenytoin and salicylates compete with thyroid hormone for TBG binding site (Kumar and Clark, 2006). .

Condition	**Concentration of binding protein**	**Total plasma thyroid hormones**	**Free plasma thyroid hormones**	**Plasma TSH**	**Clincal state**
Hyperthyroidism	Normal	High	High	Low	Hyper
Hypothyroidism	Normal	Low	Low	High	Hypo
Estrogens ***Methadone*** ***Heroin*** ***Colfibrate*** ***Major tranquilizers***	High	High	Normal	Normal	Euthyroid
Glucocorticoides ***Androgen*** ***Danazol*** ***L- asparginase***	Low	Low	Normal	Normal	Euthyroid

Table (1-2) effect of variations in the concentration of thyroid hormone-binding proteins in the plasma on various parameters of thyroid function after equilibrium has been reached

1-2-4-7: Metabolism of thyroid hormones:

The major form of thyroid hormone in the blood is thyroxine (T_4). The ratio of T_4 to T_3 released in the blood is roughly 20 to 1. Thyroxine is converted to the active T_3 (three to four times more potent than T_4) within the cells by deiodinase (5'-iodinase). These are further processed by decarboxylation and deiodination to produce iodothyronamine (T_1a) and thyronamine (T_0a) (Kirkegaard and Faber, 1998).

T_4 and T_3 are deiodinated in the liver, kidneys, and many other tissues. One-third of the circulating T_4 is normally converted to T_3 in adult human and 45% is converted to rT_3 (Ganong, 1995). The remaining 20% is conjugated with glucuronide, sulfate, deaminated, and decarboxylated to form tetraiodothyroacetic acid, or cleaved between the two rings (Engler and Burger, 1984). The thyroid secretes only about 13% of circulating T_3 and 87 % is formed by deiodination of T_4; similarly, only 5% of circulating rT_3 is secreted by the thyroid and 95 % is formed by deiodination of T_4.

Two different enzymes are involved, 5′-deiodinase catalyzing the formation of T_3 and 5-deiodinase catalyzing the formation of rT_3. T_3 and rT_3 are then converted to various diiodothyronines (Ganong, 1995). The conversion of T_4 to T_3 in the peripheral tissues is stimulated by TSH (Bennett and Brown, 2003). Deiodination of T_4 to T_3 leads to increased biologic activity, but most of other metabolites of T_4 are biologically inactive. Reverse T_3 is degraded even more rapidly than is T_3, mostly by deiodination (Engler and Burger, 1984).

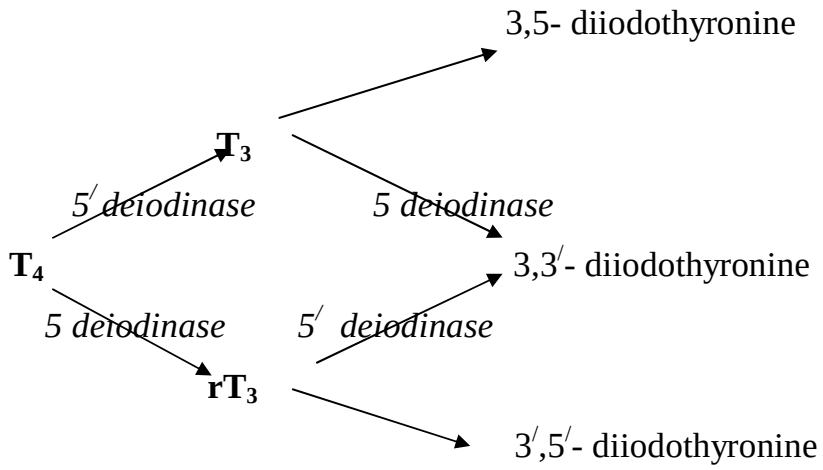


Figure (1-6) conversion of T_4 to T_3 and rT_3 and thence to diiodothyronine in liver, kidney, and other tissues.

1-2-5: Regulation of thyroid hormones secretion

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormones (TSH) from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells seems to enhance all of the processes necessary for thyroid hormones synthesis, including synthesis of the iodide transporter, thyroid peroxidase and thyroglobulin (Brent, 1994).

Thyroid function is regulated primarily by variations in the circulating level of pituitary thyroid-stimulating hormone (TSH). Normal level of TSH secretion and an adequate, but not excessive supply of iodine are indispensable for normal thyroid hormone formation (Cecil and Plum, 1996).

1-2-5-1: Chemistry of TSH:

TSH is synthesized and released by the (basophil) thyrotrophic cells of adenohypophysis (Satoskar, *et al*, 1997). Human TSH is a glycoprotein that contains 211 amino acid residues, plus hexoses,

hexosamines and sialic acid. It made up of two subunits, designed ά and β. The α subunit in human chorionic gonadotrophin (hCG) is the same as that in TSH and large amounts of hCG can activate the thyroid receptors for TSH and in some patient with benign or malignant tumors of placental origin, plasma hCG can rise to a high levels that may produce mild hyperthyroidism (Ganong,1995).

1-2-5-2: Effect of TSH on the thyroid gland:

Thyroid-releasing hormone (TRH) from the hypothalamus stimulates TSH from the pituitary, which stimulates thyroid hormone release. As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to "shutdown" of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again (Brent, 1994).

The negative feedback effect of thyroid hormones on TSH secretion is exerted at the level of the hypothalamus, but it is also in large part an action on the pituitary. When the pituitary is removed, thyroid function is depressed and the gland atrophies. The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback, as depicted in the diagram (Zhang and Lazer, 2000).

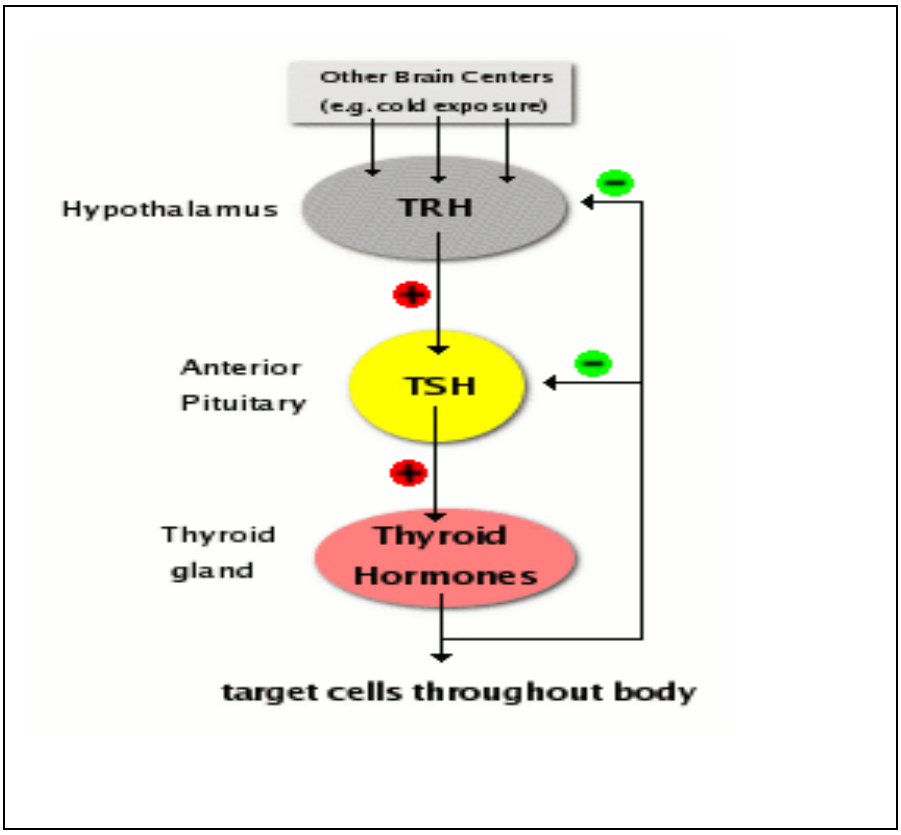


Figure (1-7) the control of thyroid hormones and negative feedback

The amount of thyroid hormone necessary to maintain normal cellular function in thyroidectomized individuals used to be defined as the amount necessary to return plasma TSH to normal. The amount of T_4 that normalizes plasma TSH in athyreotic individuals averages 112µg of T_4 by mouth per day in adults.

After a few minutes of injection TSH there are increases in iodide binding, thereby synthesis of T_3, T_4 and iodotyrosine; secretion of thyroglobulin into the colloid and endocytosis of colloid. Iodide trapping is increased in a few hours, blood flow increases and with chronic TSH treatment, the cell hypertrophy and the weight of the gland increases and becomes detectably enlarged (goitre) (Ganong, 1995).

Prolonged stimulation by TSH cause important structural changes in the thyroid: in particular a change of the epithelium from cubical to columnar proliferation of epithelium cells to form new follicles, and diminution of the volume and concentration of the colloid stored within the acini. These change my result in goitre (Bennett and Brown, 2003).

A number of other factors have been shown to influence thyroid hormone secretion. In rodents and young children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release. This makes sense considering the known ability of thyroid hormones to spark body heat production (Zhang and Lazer, 2000).

1-2-5-3: Metabolism of TSH:

TSH secretion is pulsatile; its output starts to rise at about 9.00 pm peaks at midnight, and then declines during the day. The normal secretion rate is about 110mg/dl. The average plasma level is about 2μU/ml. Thyrotrophin-releasing hormone (TRH) from the hypothalamus increases the biologic activity of TSH by altering its glycosylation. Deglycosylated TSH is removed more rapidly from the circulation; thus, its effectiveness is decreased. The biologic half-life of human TSH is about 60 minutes. TSH is degraded for most part in the kidney and to lesser extent in the liver (Ganong, 1995).

1-2-6: Effects of thyroid hormones

The thyroid hormones, tri-iodothyronine (T_3) and thyroxine (T_4) are found in all vertebrates, but it is only in the homeothermic animals that most of the effects are observed. These include stimulation of O_2 consumption, effects on growth and maturation, regulation of sugar, and lipid metabolism. The hormones furthermore influence mineral metabolism and the distribution of water and electrolytes between body fluid compartments (Capasso, *et al*, 1987).

T_3 and T_4 cross the cell membrane, probably via amino acid importing, and function via a well-studied set of nuclear receptors in the nucleus of the cell, the thyroid hormones receptors (Dartman and

Gordon, 1996). Thyroid hormones enter the cells and T_3 binds to receptors in the target cell nucleus, T_3 binds with approximately 10 times the affinity of T_4 (Murry,*et al,*1993). This is because it is less tightly bound to plasma proteins but binds more avidly to thyroid hormone receptors. The thyroid hormone-receptor complex then binds to DNA and increases the expression of the specific genes. The resultant mRNAs trigger the production of various enzymes that alter cell function (Ganong, 1995).

In contrast to steroid hormone receptors, thyroid hormone receptors bind DNA in the absence of hormone, usually leading to transcriptional regression. Hormone binding is associated with a conformational change in the receptor that causes it to function as a transcriptional activator (Brent, 1994). A major effort of T_3 is to enhance general protein synthesis and causes positive nitrogen balance. Thyroid hormones, like steroids, induce or suppress proteins by increasing or decreasing gene transcription (Murry.*et al,* 1993).

1-2-6-1: Allergenic action:

Thyroid hormones increase the rate of absorption of carbohydrates from the gastrointestinal tract. In hyperthyroidism, the plasma glucose level rises rapidly after carbohydrate meal. When the metabolic rate is increased by T_4 and T_3 in adults, nitrogen excretion is increased and if food intake is not increased, endogenous protein and fat stores are catabolized and weight is lost (Ganong, 1995).

T_4 and T_3 are influencing heat production in body tissues, uncoupling oxidative phosphorylation and increasing oxygen utilization relative to the rate of formation of high-energy phosphate bonds (Anderson, 1982). T_4 and T_3 increase the O_2 consumption of almost all

metabolically active tissues. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen and anterior pituitary. T_4 actually depresses the O_2 consumption of the anterior pituitary, presumably because it inhibits TSH secretion.

Large doses of thyroid hormones cause enough extra heat production to lead to a slight rise in body temperature, which in turn activates heat-dissipating mechanisms and peripheral resistance decrease because of continuous vasodilatation. Milk secretion is stimulated by thyroid hormones and decreased in hypothyroidism. Thyroid hormones do not stimulate the metabolism of the uterus but are essential for normal menstrual cycle and fertility (Ganong, 1995).

1-2-6-2: Effects on the nervous system:

Alterations in thyroid hormone level or responsively to thyroid hormone have significant neurologic sequelae throughout the life cycle. During fetal and early neonatal periods, disorders of thyroid hormone may lead to the development of motor and cognitive disorders. During childhood and adult life, thyroid hormone is required for neuronal maintenance as well as normal metabolic function (Sher, *et al,* 1988).

In hypothyroidism, mentation is slow and the cerebrospinal fluid (CSF) protein level elevated.The mental changes are irreversible if replacement therapy is not begun soon after birth in hypothyroid infant. The reaction time of stretch reflexes is shortened in hyperthyroidism and prolonged in hypothyroidism (Ganong, 1995).

Thyroid hormones play a critical role in development and functioning of the nervous system. Deiodinases (type 2 [D_2] and type 3 [D_3] contribute to the control of thyroid hormone action in the nervous system by regulating the local concentrations of triiodothyronine (T_3),

the main active thyroid hormone. D_2 and D_3 clearly contribute to determine T_3 concentrations depending on the area of the nervous system, the state of development, and the pathophysiologic conditions (Zrouri, 2005).

Thyroid hormones have a significant influence on the development and maturation of the central nervous system. Recently, several investigators have shown effects of thyroid hormones on myelin protein gene expression. Thyroid hormones seem to have a regulatory role with regard to life span. Hyperthyroid animals appear to have a shorter life and, at advanced age, show a myelin deficit. This may be due to the damage produced by the oxidative stress generated by an excess of thyroid hormones (Pasquini and Adamo, 1994).

1-2-6-3: Effects on the heart and kidney:

Thyroid hormones affect the functions of several organs including the heart and kidney. Using isolated left papillary muscles, the action of thyroid hormones on the mechanical and electrical properties of the heart was investigated. It was found that pure hypothyroidism causes a depression in contractile and electrical parameters (Capasso, *et al*, 1999).

Thyroid hormones increase the number and affinity of β-adrenergic receptors in the heart and consequently increase its sensitivity to inotropic and chronotropic effects of catecholamine. They also affect the type of myosin found in cardiac muscle (Ganong, 1995).

At kidney level, it was shown that thyroid hormones affect proximal tubular sodium transport and this effect is only partially mediated by the action of thyroid hormones on Na-K-ATPase activity. Using the micro puncture technique was hypothesized that the early

effect of thyroid hormone action is on the potassium permeability of proximal tubular cell membrane. This latter effect would explain the increase in isotonic fluid reabsorption through an increase in the driving force for sodium. Finally, hypothyroid patients have a decrease in glomerular filtration rate and renal plasma flow that are completely reversed by thyroxine administration. On the other hand, hyperthyroid subjects exhibit a significant increase in both parameters (Capasso, *et al,* 1999).

1-2-6-4: Effects on the skeletal muscles:

Muscle weakness occurs in most patients with hyperthyroidism (thyrotoxic myopathy). The muscle weakness may be due in part to increased protein catabolism. Thyroid hormones affect the expression of myosin heavy chain (MHC) in skeletal as well as cardiac muscle (Ganong, 1995).

The effects of thyroid hormone administration on the levels of a number of mitochondrial markers were measured in skeletal muscle and liver of normal rats. Only when rats were fed 3mg T_4 and 1mg T_3/kg diet for a 6-weaks period an increase in skeletal muscle mitochondrial markers was observed (Winder, *et al,* 1975).

1-2-6-5: Effects on the skin:

The skin normally contains a variety of proteins combined with polysaccharides, hyaluronic acid, chondroitin and sulfuric acid. In hypothyroidism, these complexes accumulate, promoting water retention and the characteristic puffiness of the skin (Myoxedema). When thyroid hormones are administered, the proteins are mobilized, and diuresis continues until the Myoxedema is cleared.

Thyroid hormones are necessary for hepatic conversion of the carotene to vitamin A, and the accumulation of carotene in the bloodstream (carotenemia) in hypothyroidism is responsible for the yellowish tint of the skin. Carotenemia can be distinguished from jaundice because in the former condition the sclera is not yellow (Ganong, 1995).

1-2-6-6: Effects on growth:

Physiological levels of circulating thyroid hormones are necessary to maintain normal pituitary GH secretion owing to their direct stimulatory actions. When the serum concentrations of thyroid hormone is increase above the normal range there is an increase in hypothalamic somatostatin tone, which in turn suppresses pituitary GH secretion and overrides any stimulatory effects. The suppression of GH secretion by thyroid hormones may be mediated at the hypothalamic level also by a decrease in GHRH release (Giustina and wehernberg, 1995).

There is a curious association between the two classes of hormones related to growth itself. T_3 and glucocorticoids enhance transcription of the growth hormone (GH) gene, so that more GH is produced. This explain classic observation in which the pituitaries of T_3-deficient animals were found to lack GH, and it may account for some of the general anabolic effect of T_3 (Murry,*et al,*1993). Thyroid hormone replacement in hypothyroidism rapidly stimulates GH mRNA synthesis, which is followed by the gradual restoration of pituitary GH stores and serum GH concentration (Wood, *et al,* 1987).

Thyroid hormone controls growth hormone synthesis in GH cells and that the induction of the growth hormone response by glucocorticoid

appears to be highly dependent on thyroid hormone action. Thyroid hormone induces growth hormone synthesis approximately 5 to 20 fold and cortisol increases this response 2 to 6 fold further (Shapiro,*et al*,1978).

Thyroid hormones are known to be important modulators of development process. Thyroid hormones are required for the conversion of a tadpole into frog, a process that involve conversion from fetal to adult hemoglobin, stimulation of urea cycle enzymes and epidermal change (Murry, *et al*, 1993).

1-2-6-7: Effects on cholesterol metabolism:

Thyroid hormones lower the circulating cholesterol levels. The decrease in plasma cholesterol concentration is due to increased formation of low-density lipoprotein (LDL) receptors in the liver, resulting in increased removal of cholesterol from the circulation (Ganong, 1995).

High affinity uptake of serum derived low-density lipoprotein (LDL) cholesterol is accomplished through the LDL receptor in the liver. In mammals, thyroid hormone depletion leads to decreased LDL receptor expression and elevated serum cholesterol (Shin and Obsorne, 2003).

1-2-6-8: Relation to catecholamines:

The action of thyroid hormones and catecholamines, epinephrine and nor epinephrine, are intimately interrelated. Epinephrine increase the metabolic rate, stimulates the nervous system and produce cardiovascular effect similar to those of thyroid hormones, although the duration of these actions is brief (Ganong,1995).

Brown adipose tissue (BAT) responses to norepinephrine are blunted in hypothyroidism and are rapidly restored by thyroid hormone. Catecholamines toxicity is markedly increased in rats treated with T_4 (Capasso, *et al*, 1999).

Some of the effects of thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamine with consequent increased activation of the reticular activating system (Murry, *et al*, 1993).

1-2-7: Measurement of thyroid hormones

Circulating levels of most hormones are very low (10^{-9} – 10^{-12}) and cannot be measured by simple chemical techniques. Thyroid hormones are therefore usually measured by immunoassays which rely on high specific antibodies which bind specific to the hormone being measured during the assay incubation.

Large amount of thyroid hormones are bound to antibody on solid phase – large amount of labeled antibody in the liquid phase. Less hormone, and therefore less labeled antibody, is linked to the solid phase (Kumar and Clark, 2006).

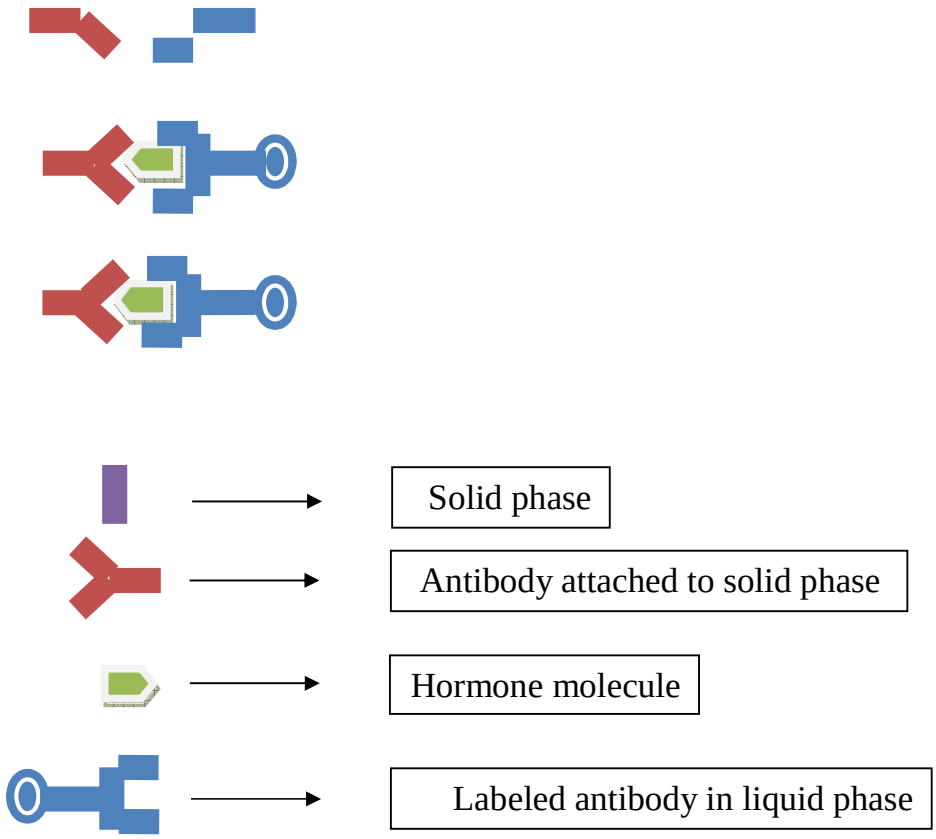


Figure (1-8) mechanism of thyroid hormones measurement.

1-2-8: Thyroid disorders

1-2-8-1: The goitre

The normal thyroid gland is impalpable the term goitre (Latin, guttur = the throat) is used to describe generalised enlargement of the thyroid gland (Mann, *et al*, 1995).Goitre is an enlargement of the thyroid gland that often produces a noticeable swelling in the front of the neck. This enlargement can be caused by iodine deficiency, inability of the body to use iodine correctly, or a variety of thyroid disorders, including infection, tumors, and autoimmune disease. Some environmental

pollutants, heavy metals poisoning, and certain drugs can also contribute to goitre formation (Precott, *et al,* 1992) and (Gaitan,1982

Figure (1-9) goitre caused by Iodine Deficiency Disorder.

Diffuse nontoxic and multinodular goitre reflects deficiency of thyroid hormones production most often due to dietary iodine deficiency followed by compensatory rise in the serum TSH level, which in turn causes hypertrophy and hyperplasia of thyroid follicular cells to correct the hormone deficiency and maintain euthyroid state at the expense of thyroid enlargement (Danish, 2005). Preschool children, adolescent girls, pregnant women, and the elderly are most vulnerable to goitre and other iodine-deficiency disorders (Ingenbleek and Visscher, 1979).

When iodine deficiency is severe, goitre appears in childhood, when it is moderate goitre appears later, occurring especially at puberty, and during pregnancy and lactation, when there is a drain on the iodine supply (Anderson, 1982).

Goitre prevalence in school-age children (SAC) is an important indicator of iodine deficiency disorders (IDDs) in the population. Goitre prevalence ≥5% in SAC indicates a public health problem (WHO, 2001). Goitre has traditionally been assessed by palpation, particularly in field studies. In the last decade, ultrasongraphy, which allows precise estimation of thyroid volume, has become the preferred method of assessment (Delang, *et al*, 1997).

1-2-8-1-1: Etiology:

The basic cause of goitre is decreased hormones production due to iodine deficiency that may be endemic or sporadic.

(a) Endemic goitre:

It is the result of chronic dietary deficiency of iodine. It occurs in geographic areas where the soil, water and food supplies contain low levels of iodine such as mountain areas. The term endemic goitre is used when its incidence in a given region reaches 10 percent or more of general population (Danish, 2005).

Very recently the cut-off point of 10 was revised downward because it was found that goitre prevalence rate between 5% and 10% may be associated with a range of abnormalities, including subnormal circulating levels of thyroid hormones and elevation of thyroid stimulating hormone (TSH) in the population, clearly representing a public concern (WHO, UNICEF & ICCIDD,1993).

The incidence of endemic goitre is decrease greatly in countries where the people use iodized salt. Much less commonly, goitrogens are responsible for endemic goitre and include cabbage, cauliflower and turnips (Danish, 2005). The causation of endemic goitre is not fully understood, but it is known that deficiency of iodine is the chief factor.

There may be contributory factors which render any iodine present unavailable such as pollution of water supplies by sulphur containing organic matter or presence of much calcium or fluoride (Anderson, 1982).

***(b) Sporadic goitre*:**

May occur anywhere and it is usually due to an increased physiologic demand for thyroxine at puberty or during pregnancy, and may be referred to as physiologic goitre.

1-2-8-1-2: Pathology:

Changes in the thyroid gland progress through diffuse enlargement to multinodular goitre.

(a) Diffuse nontoxic goitre:

Is a name given to various non-inflammatory conditions that result in enlargement of thyroid gland without hyperthyroidism. All forms of nontoxic goitre are probably preceded and for a time accompanied by a phase of impaired thyroid hormone synthesis due to; inadequate supply of iodide, impaired thyroid enzyme activity, result of genetic defect or exogenous toxic substances (Anderson,1982). In the early stages, small follicles lined by tall columnar cell characterize diffuse hyperplasia. This diffuse hyperplasia produces diffuse enlargement of thyroid gland. The term nontoxic is used because thyroid hormones level remains normal (Danish, 2005).

***(b)Multinodular goitre*:**

The follicles become distended with colloid and the lining epithelial cells become flattened or cuboidal. Nodules characterize multinodular goitre are composed of:

(i) Colloid filled- follicles indicating involution.

(ii) Areas of hyperplasia.

(iii) Fibrosis.

(iv) Areas of hemorrhage, cystic degeneration and calcification.

1-2-8-1-2: Clinical features:

(i) Patient present with painless diffuse enlargement of the gland.

(ii) Large goitre may cause airway obstruction dysphagia and compression of large vessels in the neck.

(iii) Abnormal thyroid hormone production may rarely occur in multinodular goitre.

(iv) Hyperthyroidism is common than hypothyroidism, and is due to development of autonomously functioning hyperplasic nodules in the gland (toxic nodular goitre).

(v) Multinodular goitre has a risk of development of carcinoma in small number of patients (Danish, 2005).

1-2-8-1-4: Effect of vitamins and minerals:

Iodine supplements will help to shrink goitres during early stages, but they have no effect in later stages (Cotran,*et al*,1989). Ingestion of 2,000 to 6,000 mcg of iodine daily over long periods can be toxic to the thyroid and can be a cause of goitre (Wilson,*et al*,1998).

When iodine deficiency is present, other nutrient levels become important in the development of goitre. Deficiencies of zinc (Ozata,*et al*,1999) and manganese can both contribute to iodine deficiency-related goitre; however, an animal study found that manganese excess can also be goitrogenic (Kawada,*et al*,1985). It has been suggested that selenium deficiency may contribute to goitre (Untro,*et al*,1999). However, when selenium supplements were given to people deficient in both iodine and selenium, thyroid dysfunction was aggravated, and it has been suggested

that selenium deficiency may provide some protection when there is iodine deficiency (Corvilain,*et al,*1993).

Blood levels of vitamin A are lower in people with goitre than in similar people without goitre (Keyvain,*et al,*1988). Animal research has found that, in iodine-deficient conditions, a supplement combination of vitamin C , vitamin E, and beta carotene prevented goitre formation (though hypothyroidism was not improved), and vitamin E alone had a similar effect (Mutaku,*et al,*1998).

1-2-8-1-5: Treatment of simple goitre:

Prevention and treatment of simple goitre in endemic area, the incidence of goitre has been strikingly reduced by the introduction of iodize salt. In the early stages a hyperplastic goitre may regress if thyroxine is given in adose of 0.15 – 0.2 mg daily for afew month (Mann, *et al,* 1995).

1-2-8-2: Hypothyroidism

Decreased secretion of thyroid hormone is called hypothyroidism. The effect of subnormal secretion of T_3 and T_4 vary depending upon the severity of thyroid hormone deficiency and the age of onset of the disorder. Infantile hypothyroidism is called cretinism and in the adult the syndrome is referred myxoedema (Anderson,1982).

1-2-8-2-1: Etiology

(a) Primary hypothyroidism

It is a decreased thyroid hormones production due to disease process in the thyroid gland and this is the most common type. The most common causes of primary hypothyroidism are:

(i) Removal of thyroid by surgery.

(ii) Radiation therapy.

(iii) Hashimoto's thyroiditis.

(iv) Primary idiopathic hypothyroidism.

(b) Secondary hypothyroidism

It is a decrease thyroid hormones production due to failure of pituitary TSH secretion in condition such as hypopituitarism. In this type which is rare the deficient TSH secretion leads to thyroid atrophy rather than goitre.

1-2-8-2-2: Clinical features:-

The major symptoms and signs of hypothyroidism are related to the metabolic, systemic and developmental actions of the hormones (Geown, 2003).

(a) Metabolic consequences:-

(i) Decreased basal metabolic rate (BMR).

(ii) Cold intolerance with constricted peripheries under normal temperature conditions.

(iii) Reduced appetite but increased weight.

(b) Systemic consequences:-

(i) Decreased resting heart rate.

(ii) Decreased gut motility leading to constipation.

(iii) Slowed thinking, somnolence and delayed muscle stretch reflexes.

(c) Developmental consequences:-

(i) Cretinism (in infants & children).

(ii) Myxoedma (in older children & adult).

1-2-8-2-2-1: Cretinism:

Is a term used to describe hypothyroidism occurring in infancy or early childhood, and its causes include:-

(i) Failure of development of thyroid gland (thyroid agenesis)

(ii) Failure of thyroid hormones synthesis due to severe iodine deficiency in diet of both mother during pregnancy and thereafter birth.

(iii) Failure of thyroid hormones synthesis due to goitrogens in diet.

(iv) Medication during pregnancy, such as radioactive iodine therapy.

(v) Maternal autoimmune disease. (Bongers,*et al*,2000)

The term endemic cretinism is used to describe clusters of infants with goitre and cretinism in defined geographic areas. These areas were discovered to be low in iodine, and the cause of endemic cretinism was determined to be hypothyroidism secondary to iodine deficiency. The term sporadic cretinism was initially used to describe the random occurrence of cretinism in no endemic areas. The cause of these abnormalities was identified as nonfunctioning or absent thyroid glands (Delange,1996). Sporadic cretinism is due to complete or near complete failure of thyroid development the parents and other children may be perfectly normal. In endemic area, goitrous cretinism is common , and is due to maternal and fetal iodine deficiency (Mann, *et al*, 1995).

Mild iodine deficiency has been reported to reduce intelligence quotient (I.Q.) by 10 - 15% and cause increased rates of stillbirths, prenatal and infant mortality (Marberly,*et al*,1994). Cretinism being subdivided into neurologic and myxoedematous types and both can be prevented by adequate maternal and infant iodine intake (Boyages,*et al*,1997).

Manifestations of neurologic cretinism:

(i) Dwarf with severe mental defect.

(ii) Disproportionately short limbs.

(iii) Coarse dry skin.

(iv) Deficient hair and teeth.

(v) A large protruding tongue.

(vi) Pot belly with umbilical hernia.

(vii) Retardation of both growth and maturation of skeleton.

(viii) The epiphyses may be irregular and radiologically stippled.

Unless replacement therapy with T_3 and T_4 commences early, the change especially; the mental defect become irreversible, though there may be some improvement in physical appearance (Anderson,1982).

1-2-8-2-2-2: Myxoedma:-

Severe hypothyroidism, especially in the elder, may present with confusion or even coma myxoedma coma is very rare (Kumar and Clak, 2006). May be the end result of number of disease of the thyroid gland or it may be secondary to pituitary failure (pituitary hypothyroidism) or hypothalamic failure (hypothalamic hypothyroidism) (Ganong,1995). The most common cause is Hashimoto's thyroiditis and the other causes are antithyroid drugs, surgical removal of the gland, dietary iodine deficiency, obesity and pituitary failure (Danish, 2005).

Manifestations of myxoedema:-

Symptoms;

(i) Generalized apathy.

(ii) Mental sluggishness.

(iii) Loss of hair.

(iv) Cold intolerance.

(v) Constipation.

(vi) Plasma cholesterol is elevated.

The voice is husky and slow, the basis of the aphorism is that "myxedema is one of the disease that can be diagnosed over the telephone". In some patient there are severe mental symptoms "myxedema madness" (Ganong , 1995).

Signs;

Deposition of increased amount of mucopolysaccharide in connective tissues producing the following features:-

i- Skin: producing peculiar diffuse non pitting edema.

ii- Larynx: causing hoarseness of voice.

iii- Heart: causing cardiac enlargement and pericardial effusion.

iv- Tongue: producing enlargement of the tongue (Danish, 2005).

Figure (1-10): Myxedematous endemic cretinism. Four inhabitants aged 15-20 years: a normal male and three females with severe longstanding hypothyroidism with dwarfism, retarded sexual development, puffy features, dry skin and hair and severe mental retardation.

1-2-8-2-2-3: Congenital hypothyroidism:

Congenital hypothyroidism is a condition where a newborn has decreased or absent thyroid function and thyroid hormone production. In most cases, the cause of congenital hypothyroidism is unknown. A small percentage of cases are inherited and caused by mutations in the genes producing the enzymes (proteins) required for thyroid hormones synthesis (Bongers,*et al*,2007).

Most studies of congenital hypothyroidism suggest a female to male ratio of a 2:1. The ratio is lower among black infants (Lorey and Cunningham,1992 & Devos,*et al,* 1999).

Diagnosis: At birth, most infants are screened for congenital hypothyroidism. A pediatric endocrinologist is appropriate if a specialist is needed. Tests may include measurement of free (unbound) thyroxine (T_4) levels in the blood, measurement of thyroid stimulating hormone

(TSH) in the blood and Thyroid scan (technetium) (American Academy, 2006).

Treatment: If untreated, congenital hypothyroidism can lead to severe mental retardation and growth retardation. However, if caught early at birth (preferably during the first two weeks of life) when the brain and nervous system are not yet fully developed, thyroid hormone replacement could prevent this system from damage.

Congenital hypothyroidism is generally treated with hormone replacement therapy. The hormone thyroxine is given in one of these forms; levothyroxine, levothroid, levoxyl or synthroid (LeFranchi and Austin, 2007)**.**

1-2-8-2-3: General investigations of hypothyroidism:-

(1) Serum free T_4 level which will found to be low.

(2) Serum TSH which may either be;

(i) Elevated in primary hypothyroidism.

(ii) Low in secondary hypothyroidism (Danish, 2005).

1-2-8-2-4: Treatment of hypothyroidism:

Thyroxine is replacement therapy. Iodine supplementation can be an effective treatment of iodine deficiency hypothyroidism and can halt the growth of goitre if the cause is not complicated by malnutrition or environmental and dietary goitrogens (Lee,*et al*,1999).

1-2-8-3: Hyperthyroidism

Is an excessive secretion of thyroid hormones and usually T_4.

1-2-8-3-1: Etiology:-

(*a) Primary:-*

It is the most common type in which excessive secretion of thyroid hormones is due to primary abnormality in the thyroid gland and its causes include:

(i) Graves disease in more than 95%.

(ii) Hyperfunctioning follicular adenoma.

(iii) Hyperfunctioning multi-nodular goitre.

(iv) Ingestion of excessive exogenous thyroid hormone for hypothyroidism.

(v) Thyroiditis in an early stage.

(b) Secondary:-

When the excessive secretion of hormone due to an abnormality outside the thyroid gland. The causes include:

(i) TSH secreting pituitary adenoma.

(ii) Ectopic thyroid hormones secretion by ovarian teratoma (Danish, 2005).

1-2- 8-3-2: Clinical features:-

(a) Metabolic consequence:

Dramatic elevation of basal metabolic rate is increased heat production, heat intolerance and sweating. Appetite increased but weight declines.

(b) Systemic consequence:-

(i) Rapid heart rates and arrhythmias.

(ii) Abnormal breathlessness during exercise.

(iii) Increased gut motility (Diarrhoea).

(iv) Mental over activity.

(v) Nervousness, anxiety, insomnia and tremors.

(vi) Menorrhea and infertility.

(vii) Muscle weakness and osteoporosis with bone pain.

(c) Developmental consequence:-

(i) In children there is early closure of the epiphyseal plates in long bones.

(ii) In adults the stature is reduced (Geown, 2003).

1-2-8-3-3: Investigations of hyperthyroidism:-

(i) Serum free T_4 is elevated.

(ii) Serum TSH is decreased in primary hyperthyroidism and elevated in secondary hyperthyroidism.

1-2-8-3-4: Treatment of hyperthyroidism:-

(i) Antithyroid drugs.

(ii) Subtotal thyroidectomy.

(iii) Radio iodine.

1-2-8-4: Autoimmune thyroiditis:

A family of Ig G immunoglobulines, collectively known as thyroid-stimulating antibodies (TsAb) activates TSH receptors on the

follicular cell membrane. They have a more protracted action than TSH and are responsible for virtually all cases of thyrotoxicosis (Mann, *et al*, 1995).

Serum antibodies to the thyroid are common and may be either destructive or stimulating; both occationally coexist in the same patient. Destructive antibodies may be directed against the microsomes or against thyroglobulin the antigen for thyroid microsomal is the thyroid peroxidase (TPO) enzyme. TPO antibodies are found in up to 20% of the normal population, especially older women (Kumar and Clark, 2006). In this condition, there is infiltration of the thyroid gland by lymphocytes and plasma cells associated with abnormalities of the thyroid epithelium (Anderson,1982).

1-2-8-4-1: Graves' disease (exophthalmic goitre)

Is the most common cause of endogenous hyperthyroidism, which results from the production of thyroid -stimulating IgG (TSI) that activates the TSH receptor. This causes a diffuse enlargement of the thyroid gland and excessive, uncontrolled production of T_3 and T_4 ,since the production of TSH is not under feedback control (Murry,*et al*,1993).

Now seems clear that Grave's disease is an autoimmune disease in which T lymphocytes activated by antigens in the thyroid gland stimulate B lymphocytes to produce circulating antibodies against the antigen (Ganong,1995).

Differentiating two common forms of hyperthyroidism such as Graves' disease and toxic multi-nodular goitre is important to determine proper treatment. The disease occurs most frequently in women (female: male = 7:1). It occurs most commonly in the third to fifth decades of

life, but is not uncommon in adolescents, during pregnancy, at the time of menopause and in people over age 50.

There is a marked family preponderance, which has led to speculation that there may be a genetic component. To date, no clear genetic defect has been found that would point at a monogenic cause (Wallschofski,*et al*,2004). Any mother with a history of Graves' disease may have circulating TSI. Even if she has been treated (eg. by surgery), the immunoglobuline may stil be present to stimulate the fetal thyroid, and the fetus can thus become hyperthyroid, while the mother remains euthyroid (Kumar and Clark,2006)

1-2-8-4-1-1 Etiology:-

It is an autoimmune disease characterized by the presence in the serum of autoantibodies of the 1gG class directed against the TSH receptors in the thyroid cells. The combination of the antibody with the receptor leads to stimulation of the cell to produce thyroid hormones. The antibodies are long-acting thyroid stimulator (LATS). The antibodies cross the placenta in pregnancy and stimulate the fetal thyroid, causing neonatal hyperthyroidism. (Danish, 2005).

1-2-8-4-1-2: Clinical features:-

(i) Diffuse enlargement of thyroid gland that appears as a mass in the neck.

(ii) Opthalmopathy characterized by;

a- Wide, staring gaze, lid lag, wide-open eyes, decreased blinking and reduced eye movement.

b-Exophthalmos (proptosis) due to deposition of mucopolysaccharide in rich connective tissue behind the eyeball leading to protuberance of eyeball.

(iii) Dermopathy (pretibial Myxoedema) characterized by localized areas of thickening and hyperpigmentaion of the skin over the anterior aspect of feet and legs (Danish, 2005).

Thyrotoxicosis place a considerable load on the cardiovascular system, and in some patient with hyperthyroidism most or even all of the symptoms are related to cardiovascular system (Ganong,1995).

1-2-8-4-1-3: Investigations:-

(i) Elevated T_3, T_4 and depressed TSH.

(ii) Radioiodine scan shows diffuse uptake of iodine.

Thyroid-stimulating antibodies are detectable in the blood of most untreated patients by an invitro test, in which the patient serum competitively inhibits the binding of labeled TSH to human thyroid cell membrane (Danish, 2005).

Thyroid stimulating antibodies explain the failure to:

(i) Demonstrate TSH in the serum of patient with grave disease.

(ii) Suppress thyroid activity by administration of T_3 to these patients (Anderson**,** 1982).

1-2-8-4-1-4*: *Treatment:-

Grave's disease is treated by blocking hormone production with an antithyroid drug, by ablating the gland with a radioactive isotope of iodide (such as ^{131}I), or by a combination of these two methods. Occasionally, the gland is removed surgically (Murry,*et al*,1993).

1-2-8-4-2: Hashimoto's thyroiditis:-

It is autoimmune thyroiditis, again more common in women and most common in late middle age (Kumar and Clark, 2006). Some of the

antibodies damage the thyroid gland, producing Hashimoto's thyroiditis and this condition can progress to hypothyroidism. It is responsible for most cases of primary hypothyroidism (Ganong, 1995).

1-2-8-4-2-1: Etiology:-

It is believed to be the result of an autoimmune response against the thyroid gland. The most likely mechanism of thyroid cell destruction is a cytotoxic T-cell mediated hypersensitivity reaction.

1-2-8-4-2-2: Pathology:-

In the early stage, the thyroid gland is diffusely enlarged and as the disease progresses the gland becomes smaller and the end result is markedly atrophic, fibrosed thyroid gland. Microscopically there is evidence of destruction of thyroid follicles associated with severe lymphocyte infiltration of the gland (Danish, 2005)..

1-2-8-4-2-3: Clinical features:-

Patient usually has firm goitre of moderate size. Hypothyroidism is in about half cases. The thyroid uptake of iodine is reduced and orginification is impaired and an abnormal iodinated thyroprotein is sometimes found in the serum (Kumar and Clark, 2006). Thyroid auto antibodies can be detected in the serum of almost all patients.

1-2-8-4-2-4: Risk factors

A risk factor is something that increases your chance of getting a disease or condition. Risk factors include (American association, 2002):

(i) Age: risk increases with age, especially over 65 years old.

(ii) Sex: female to male ratio is 5-10:1.

(iii) Genetics: multi-glandular autoimmune syndrome.

(iv) Ethnicity: Caucasian, Hispanic.

(v) History of family members with hypothyroidism.

(vi) History of other autoimmune diseases:

a- Pernicious anemia.

b- Type 1 diabetes mellitus.

c- Under active adrenal or parathyroid glands.

f- Lupus.

1-2-8-4-2-5: Diagnosis:

(i) Medical and family history.

(ii) Physical examination.

(iii) Blood tests to confirm the diagnosis, which include thyroid stimulating hormone (TSH), free T_4 and free T_3, and antibodies that attack the thyroid gland (Surks,*et al*,2004).

1-2-8-4-2-6: Treatment:

In the early stages of Hashimoto's thyroiditis, there is no specific treatment. However, most people with this condition eventually develop hypothyroidism. At that point, you will need to start taking medication (levothyroxine and/or triiodothyronine) that replaces the thyroid hormones (Escobar,*et al*,2005).

1-2-8-5: Tumors of the thyroid:

A thyroid tumor is a cystic or solid mass that occurs in the thyroid. Thyroid tumors are either benign (noncancerous) or malignant

(cancerous) growths. Examples of benign tumors are adenomas, which secrete thyroid hormone. Malignant tumors are rarer and are more common in women than in men. A cancerous thyroid tumor, known as thyroid carcinoma, can metastasize (spread) to other parts of the body (UMMC, 2006).

1-2-8-5-1: Benign tumors (Adenoma):-

Follicular adenoma of the thyroid is the commonest neoplasm of the gland, accounting for about 30% of all cases of solitary thyroid nodules. It may occur at any age and females are 4 times more affected than males (Danish, 2005). These tumors present varying appearance depending on the extent of degenerative change, amount of colloid storage and they may be hemorrhagic or cystic (Anderson, 1982).

1-2-8-5-1-1: Clinical features:-

(i) Painless mass.

(ii) Large masses may produce local symptoms such as difficulty in swallowing.

(iii) Usually euthyroid.

1-8-5-1-2: Investigations:-

(i) Radionuclide's scan.

(ii) Fine needle aspiration and cytology.

(iii) Ultrasounds scan (Danish, 2005).

1-2-8-5-2: Malignant tumors (Carcinoma):-

Is invades surrounding structure, including the trachea and recurrent laryngeal nerves and death is commonly due to asphyxia (Anderson,1982). Mostly occurs in adult. Females are more affected than males. Exposure to ionizing radiation, particularly during the first

two decades of life is an important predisposing factor (Murry, *et al*, 1993).

1-2-8-5-2-1: *Types of carcinoma:-*

Thyroid carcinoma is classified based on its microscopic appearance into 4 types:-

(i) Papillary Carcinoma:-

Is most common and it affects females 3 times more than males. Peak age is 15 – 35 years. It present as a mass in the anterior aspect of the neck, which grows very slowly (Danish, 2005). Sometimes seen in children and young adults in whom there is often a history of local x–irradiation. The tumour is not well encapsulated and is sometimes only few millimeters in diameter (Anderson,1982).

(ii) Follicular carcinoma:-

Malignancy is recognized by invasion of the fibrous capsule and blood vessels. It is the second most common form of thyroid carcinoma. Female are more affected with peak incidence at middle age (Danish, 2005). Some of this tumor take up ^{131}I which can be used therapeutically (Anderson,1982).

(iii) Medullary Carcinoma:-

They derived from calcitonin-secreting parafollicular cells (C cell). In some cases, tumour cells secrete other polypeptide hormones such as somatostatin, serotonin and vasoactive intestinal peptide (VIP).

Majority of cases of medullary carcinoma present as a mass in the neck, which may metastasize via the blood stream and are usually aggressive. In some patients initial manifestation may be due to polypeptide hormone secretion eg. Diarrhoea is due to secretion of VIP. Calcitonin in blood is elevated (Danish, 2005).

(iv) Anaplastic Carcinoma:-

It is one of the most aggressive human neoplasms occurring predominantly in elderly particularly in areas of endemic goitre. Death usually occurs within a year after diagnosis and is mainly due to local invasion of neck structures (Danish, 2005).

1-2-8-6: Other thyroid disorders

1-2-8-6-1: Degenerative changes:-

Excluding changes in nodular goitre and tumour degenerative changes in the thyroid, they are comparatively rare and are of little importance. Amyloid disease may affect the thyroid gland either alone or as part of widespread amyloidosis. When well marked, it cause thyroid enlargement (amyloidal goitre). Amyloid is found in the stroma of medullary carcinoma of the thyroid.

1-2-8-6-2 Congenital abnormalities:-

Occasionally a mass of thyroid tissue is found in the base of the tongue (lingual thyroid) and thyroid may then be absent from it is normal size. Congenital absence and hypoplasia of the thyroid are among the causes of sporadic cretinism (Anderson,1982).

1-2-8-6-3: Thyroid hormone resistance:-

Thyroid hormone resistance is an inherited condition caused by an abnormality of the thyroid receptors. Mutation to the receptors results in the need for high levels of thyroid hormone to achieve the same intra cellular effect. As a result, the normal feedback control mechanism result in high blood levels of Thyroxine with normal TSH in the order to maintain a euthyroid state (Kumar and Clark, 2006).

1-2-8-6-4: Dishormongenesis:

Geentically determined deficiencies in the enzymes controlling the synthesis of thyroid hormones, if severe , are responsible for goitre formation with hypothyroid.if moderate degree, a simple (euthyroid) goitre results. Similarly goitrogens may produce a goitre with, or without hypothyroid.

When the thyroglobulin is broken down, uncoupled iodotyrosine are liberate as well as T_3 and T_4. they are broken down by the enzyme dehalogenase and iodine retained will in the thyroid. If dehalogenase is deficient, iodtyrosine pass into the blood, are excreted in the urine and

this may result in iodine deficiency and goitre formation. Other class of dyshormongenesis is Pendred's syndrom, when goitre is associated with congenital deafiness. This is due to a deficiency of peroxidase; the enzyme responsible for organification of trapped iodine (Mann, *et al*, 1995).

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Table (1-3): The relation between thyroid disorders and thyroid hormone c

o n c e n

Condition			Thyroid gland	Thyroid hormones	TSH
Hyperthyroidism	***primary***	Graves' disease	Diffuse enlargement	High	Depressed markedly
		Toxic nodular goitre	Multinodular goitr	High	Low
		Toxic adenoma	Solitary nodule	High	Low
		Subacute thyroiditIs	Tender enlargement	High	Normal
	Secondary	Pituitary thyrotrophic adenoma	Diffuse enlargement	High	High
Hyperthyroidism	***primary***	Thyroid agenesis	Absent	Absent	High
		Enzyme deficiency	Diffuse enlargement	Low	High
		Hashimoto's thyroiditis	Diffuse enlargement	Low	High
		Iodine deficiency	Diffuse nodular goitre	Low	High
	Secondary	Pituitary faliure	Atrophy	Low	High

1-2-9: Thyroid investigation:

(i) ***Thyroid function:*** The thyroid functional status should be established by estimation of serum thyroid hormones and TSH.

(ii) ***Autoantibody titer:*** The autoantibody status is important in determining which swellings may be manifestation of chronic lymphoic thyroiditis.

(iii) ***Isotopes scan:*** Isotopes scanning used to be the mainstay of investigation of discrete thyroid swelling to determine the functional activity relative to the surrounding gland according to isotopes uptake.

(iv) ***Ultrasnography:*** Is widely used as a noninvasive supplement to clinical examination in determining the physical charactersitics of thyroid swellings.

(v) ***Fine-needle aspiration cytology (FNAC):*** FNAC has become established as the investigation of choice in discrete thyroid swelling. FNAC has excellent patient compliance, is simple and quik to perform in the deviation outpatient department and is readily repeated.

(vi) ***Radiology:*** Chest and thoracic inlet radiographs are only necessary when there is clinical evidence of tracheal deviation or compression or retrosternal extension.

(vii) ***Large bore needle (Trucut) biopsy:*** Trucut biopsy has a high dignostic accuracy but has poor patient compliance and may be associated with complications such as pain, bleeding, tracheal and recurrent laryngeal nerve damge (Mann, *et al,* 1995).

1-2-10: Thyroid disorders therapy

1-2-10-1: Antithyroid drugs (thioamides):

The important belonging to this group are methyl and propylthiouracil ,methimazole and carbimazole. Therapeutic uses of this drugs for treatment of hyperthyroidism (Satoskar, *et al,* 1997). These drugs are:-

(i) Compete with tyrosine residues for iodine and become iodinated.

(ii) Inhibit the biosynthesis or alter the structure of thyroglobulin.

(iii) Inhibit $5^{/}$ deiodinase, reducing the conversion of T_4 to T_3 outside the tissues.

(iv) Inhibit the iodination of monoiodotyrosine.

(v) Effect on coupling by lower doses than effect iodination.

(vi) Increase radioactive iodine uptake and increase TSH secretion.

The most dangerous side-effect is agranulocytosis (1/250, more in PTU); this is an idiosyncratic reaction which does not stop on cessation of drug (Glinoer,*et al*,2001).

1-2-10-2: Iodide:

Iodide is the oldest remedy for thyroid disorders including hyperthyroidism. Its action becomes apparent within 24 hours. The BMR falls at a rate comparable to that seen after subtotal thyroidectomy (Satoskar, *et al,* 1997). Large doses (in normal individual) act directly on the thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis. It reduces the effect of TSH on the gland by reducing the cAMP response to this hormone or/ and it inhibits proteolysis of thyroglobulin (Ganong, 1995).

The hyperthyroid state is, however, only partially controlled by iodide and after a variable period, the beneficial effects seem to wear off. Within continued treatment, hyperthyroidism may return in its initial intensity (Satoskar, *et al,* 1997).

1-2-10-3: Therapeutic uses of thyroid hormones:

In cretinism, therapy must be started as soon after birth as possible, preferably within 4 weeks. With proper treatment, normal physical development and linear growth can be achieved. In adult hypothyroidism, a complete reversal of the physical and metabolic abnormalities can generally achieve by adequate replacement therapy, unless the patient proves intolerant of such therapy. This is likely to happen in patients with coronary heart disease in whom angina may be precipitated or aggravated by thyroxine. (Satoskar, *et al,* 1997).

1-2-10-4: Radioactive iodine uptake:

Diagnosis and therapy of thyroid diseases are firmly based on the principles of thyroid hormones physiology and biochemistry. The availability of radioisotopes of iodine has greatly aided in the elucidation of these principles. Radioactive iodine, because it localizes in the gland (Murry,*et al*,1993).

Iodine uptake is used as an index of thyroid function, that can be easily measured by using trace doses of radioactive isotopes of iodine that have no known deleterious effect on the thyroid. The trace is administered orally and thyroid uptake determined by placing a gamma ray counter over the neck. The isotope of iodine used is ^{123}I because it has a half-life of only 0.55 day, compared with ^{131}I which has a half-life of 60 days (Ganong, 1995).

1-2-10-5: Surgery:

In diffuse toxic goitre and toxic nodular goitre overactive internodular tissue, surgery cures by reducing the mass of overactive tissue. Surgery cures by moving all the overactive thyroid tisse: this allows the suppressed normal tissue to function again (Mann, *et al*, 1995)

Thyroidectomy should be performed only in patient who have previously been rendered euthyroid. Indications for either surgery or radioiodine are:

(i) Patient choice.

(ii) Persistent drug side-effect.

(iii) Poor compliance with drug therapy.

(iv) Recurrent hypothyroidism after drugs.

Particular indications for surgery; a large goitre, which is unlikely to remit after antithyroid medication (Kumar and Clark, 2006).

1-3: Iodine Deficiency Disorders (IDD)

Iodine insufficiency disturbs thyroid function and depending on the duration and severity of the deficiency, a range of complications and changes take place within the body, which is addressed by the term (Iodine Deficiency Disorders) (Cecil and Pulm, 1996). In 1983, Hetzel used the term ‘‘iodine deficiency disorders’’ to encompass a series of clinical and functional disorders, which include goitre, low birth weight, miscarriage, and different degrees of hypothyroidism (Hetzel, 1983).

The disorders that result from iodine deficiency are preventable by appropriate iodine supplementation; they continue to occur because of various socio- economic, cultural and political limitations to adequate iodine supplementation programmes (Volpe, 1988). Iodine deficiency occurs when iodine intake falls below the recommended levels, a natural phenomenon occurring in many parts of the world. When iodine intake falls below recommended levels the thyroid may no longer be able to synthesize sufficient amounts of thyroid hormone (Geneva, 2001).

Iodine deficiency disorders constitute one of the major health problems as the single most important preventable causes of mental handicap in the world today (Editorial, 1986). Iodine deficiency is the main etiology factor of endemic goitre (Stanbury, *et al*, 1954). Communities living in iodine-deficient environment face a major block to their human and social development. Correction of iodine deficiency is indicated as a major contribution to development (Hetzel, 1993).

Mild iodine deficiency has been reported to reduce intelligence quotient (I.Q.) by 10 - 15 % and cause increase rates of stillbirth, prenatal mortality, and infant mortality. Iodine supplementation given to school-age children can improve performance on tests of intellectual

functioning (Meberly, 1994). It is important to note that disastrous complications of IDD such as low learning capability and diminished functionality due to brain development and cognitive function disturbances may present a major problem in succeeding generation and different aspects of progress of country. In addition, it is so important that these problems are incurable but easily preventable (Editorial, 1986).

1-3-1: Prevalence of IDD in the world:

On the most recent evaluation, iodine deficiency currently represents a significant public health problem for 1575 million people (almost 30% of the world's population) in 110 countries. 655 million are affected by goitre, 20 million are believed to be significantly mentally handicapped as a result of iodine deficiency which is therefore the most prevalent preventable cause of impaired intellectual development in the world today (Volpe,1998).

Significant iodine deficiency has been found in coastal areas, large cities, highly developed countries and where IDD have been considered to be eliminated, by either prophylactic programmes or general dietary changes (Geneva, 2001). The United Nations estimate 1.7 billion people around the world are at risk of iodine deficiency disorder, including 43 million newborn babies (Geneva, 2006)

In Latin America the problem persists in Bolivia, Peru, Ecuador and many other countries, in spite of attempts to control IDD with iodized salt. IDD persist in many European countries including Germany (both F.R.G. and G.D.R.), Romania, Poland, Spain, Portugal and Italy. IDD is rare in North America because iodine is added to salt and persists

in Europe because less iodine is added to the salt in some countries (Burdoux, *et al,* 1978).

In the Southeast Asia Region eight countries; Bangladesh, Bhutan, Burma, India, Indonesia, Nepal, Sri Lanka and Thailand - all have significant IDD problems. Altogether in these eight countries, it has been estimated in the light of extensive surveys that 277 million are at risk of IDD, some 102 million have goitre, 1.5 million are cretins, and many more suffer from some degree of mental or motor impairment as a result of iodine deficiency (Clugston and Hetzel, 1994).

In Africa, goitre is endemic in many countries, notably Congo, Uganda, Kenya, and Sudan; the prevalence of goitre is as high as 81% in some parts of these countries (Ekpechi , 1987). Although iodine deficiency is the main factor in the etiology of endemic goitre, the additional role of goitrogens has been shown or suspected in areas such as Congo (Bourdoux, *et al,* 1978) and Sudan (Osman, *et al,* 1981), in which goitre is endemic. As a whole, however, the role of goitrogens is often disregarded.

In certain a region of (Africa, south America) the effect of iodine deficiency is magnified by consumption of foodstuffs such as cassava roots that contain cyanoglucosides; these substances are metabolized to thiocyanate, which has antithyroid properties (Burdoux, *et al,* 1978).

1-3-2: Prevalence of IDD in the Eastern Mediterranean Region:

Before 1987, iodine deficiency was not considered an issue of major importance in the countries of the Eastern Mediterranean Region (EMR). Despite the high rates in many areas of many countries of the region, goitre was regarded as being strictly restricted to certain geographical areas and thus not considered as an important public health

problem (Baghchi and Rejeb, 1987). Progress began with a systematic national study of goitre and other iodine deficiency disorders (IDD) in the Islamic Republic of Iran in 1983, the first country to be declared IDD-free by WHO (Azizi and Mehran, 2004).

In the Eastern Mediterranean Region (EMR) of WHO at least 10 of the 22 member states (Afghanistan, Egypt, Islamic Republic of Iran, Libyan Arab Jamahiriya ,Lebanon, Pakistan, Syrian Arab Republic, Sudan and Tunisia) have high to alarming rates of prevalence of goire in certain areas (WHO,1990). The status of IDD in the EMR countries was as follows (Azizi and Mehran, 2004):

(i) IDD under control: Islamic Republic of Iran and Tunisia.

(ii) Mild IDD: Jordan, Lebanon, Libyan Arab Jamahiriya, Egypt, Palestine, Oman, Bahrain, Qatar, Syrian Arab Republic, United Arab Emirates, Kuwait and Yemen.

(iii) Moderate IDD: Morocco, Sudan and Saudi Arabia.

(iv) Severe IDD: Iraq, Afghanistan and Pakistan.

1-3-3: Prevalence of IDD in Sudan:

In Sudan, it is estimated that about 14 million inhabitants are at risk of iodine deficiency (Elnager, *et al*, 1995). In Sudan, endemic goitre and iodine deficiency disorders are serious health problems in many areas. The prevalence of goitre among schoolchildren was estimated to be 85% in the Darfur region in western Sudan, 74% in the Kosti area in the center of Sudan, 13.5% in Portsudan in eastern Sudan, and 17% in the capital, Khartoum (Eltom, 1984).

Little is known about the prevalence of goitre in other areas of Sudan. In the areas studied so far, iodine deficiency was identified as the principal etiologic factor. However, consumption of pearl millet, vitamin

A deficiency, and protein-energy malnutrition were also suggested as instrumental factors in the etiology of endemic goitre in western Sudan (Elnour, *et al,* 1997).

According to the WHO reports, more than 800 million individuals in the world are suffering from IDD (Geneva, 1999). Despite its efforts, the WHO has not been able to completely eliminate iodine deficiency throughout the world. As a result, endemic goitre and cretinism are still observed in some areas (Murdoch, *et al,* 1999).

1-3-4: The importance of iodine deficiency disorders (IDD):

Iodine deficiency, through its effects on the developing brain, has condemned millions of people to a life of few prospects and continued underdevelopment. The most critical period is from the second trimester of pregnancy to the third year after birth. In its extreme form, the result is cretinism, but of much greater public health importance are the more subtle degrees of brain damage and reduced cognitive capacity, which affect the entire population (Geneva, 2001).

The important consequences of iodine deficiency are goitre, hypothyroidism, mental retardation, cretinism and increased neonatal and infant mortality (Kopp, *et al*, 1994).

1-3-5: Classification of risk of iodine deficiency disorders:

The proportion of subjects classified as being at risk from IDD according to three different criteria was calculated: ranges of iodide concentration in urine (World Health Organization, 1994); iodide: creatinine ratios (National Research Council, 1989); and daily iodide excretion according to criteria adapted from Clugston and Hetzel (1994).

The latter criterion is based on epidemiological work indicating that endemic goitre is likely to appear in populations with iodide excretions less than 50µg/d, and endemic cretinism in those with less

than 25µg/dl (National Research Council, 1989, Glugston, *et al*.1994 & WHO, 1994).

1-3-6: Treatment and prophylaxis of iodine deficiency disorders:

Prolonged administration of iodide or of thyroid hormone has been found highly effective in reducing the size of endemic goitre. Surgical treatment is often justified in large goitres with pressure symptoms. Some options for correction of IDD may have to be considered, such as:

1-3-6-1: Iodized salt:

In 1994, WHO produced a document in collaboration with UNICEF and ICCIDD to provide guidance concerning the use of surveillance indicators of IDD. Salt iodization has been recommended as the preferred strategy to control and eliminate IDD. Salt must reach the entire affected population, in particular those groups that are most susceptible; pregnant women and young children. The groups most susceptible to IDD; pregnant and lactating women, and infants may need iodine supplementation when universal salt iodization is not fully implemented (ICCIDD, 2008).

Iodized salt can be used to prevent IDD and it improves the health situation of people with IDD (Geneva, 2001). Administration of iodized salt has proven a useful method for correcting an iodine deficient diet and has been widely used in prevention of endemic goitre (Marine and Kimball, 1917 & Burgi,*et al*,1990). This method is difficult to apply in place where, for socioeconomic reasons, the general infrastructure is unable to ensure a systemic distribution of iodized salt to whole population (Lmberg, 1985).

Adding iodine (as potassium iodide or iodate) during the packaging or processing of salt is technically easy and the cost is low ,

in hot tropical climates or suboptimal conditions of purity or storage , potassium iodate is preferred over iodide because it is more stable (Buttfield and Hetzel,1967). Iodine concentration in salt at the point of production should be within the range of 20-40 mg of iodine per kg of salt. The iodine should be added as potassium (or sodium) iodate. Under these circumstances, median urinary iodine levels will vary from 100 - 200 µg/l (Geneva, 2001).

Countries, or areas within countries, can be categorized into four groups based on the proportion of household use of iodized salt at the national level (ICCIDD, 2008).

***Group 1*:** Countries, or areas within countries, in which more than 90% of the households have access to iodized salt. The countries in this group should sustain the achievement of USI and periodically reassess the salt iodization program and population iodine status.

***Group 2*:** Countries or areas are within countries, in which 50 - 90% of the households have access to iodized salt. The countries in this group should make efforts to accelerate salt iodization based on the existing operational guidelines.

***Group 3*:** Countries or areas are within countries, in which 20-50% of the households have access to iodized salt. The countries in this group will need to assess the feasibility of increasing iodine intake in the form of a supplement or iodine-fortified foods by the most susceptible groups.

***Group 4*:** Countries or areas are within countries, in which less than 20% of the households have access to iodized salt. Each country in this group should assess the current situation of its salt iodization program to identify national or sub-national problems and to update its strategies and action plans.

1-4-6-2: Iodized oil:

Iodized oil, because of its high iodine content, can be used as a treatment for the prompt correction of hypothyroidism. Because of the different effects of iodized salt and iodized oil, these two methods can be used together. Use of iodized oil has shown many positive effects in iodine-deficient populations. Iodized oil may successfully be given to pregnant women in the first month of pregnancy since brain development of the fetus takes place during this period of pregnancy (Geneva, 2001).

Iodized oil is more expensive than salt and requires direct administration to each subject, if given intramuscularly; it requires skilled administration (Wolff, 2001).

Systemic effects of iodized oil are very high urinary iodine excretion in the first days after injection and rapid decrement of TSH, which thereafter decreases slowly with improvement in hearing threshold. The side effects of iodized oil treatment include thyrotoxicosis, hypothyroidism and skin problems (Geneva, 2001).

1-3-6-3: Iodine solution:

Administration of iodine solutions, such as Lugol`s iodine, at regular intervals (once a month) is sufficient (Geneva, 2001).Oral administration of potassium iodide solution every two to four weeks or daily administration of tablets containing from 100 - 300µg potassium iodide is also sufficient (Wolff,2001).

1-3-6-4: Iodized water:

The iodization of water supplies is by direct addition of iodine solution or via a special delivery mechanism (WHO, 2000). The

technology is as simple as adding a few drops of iodine (not iodide or iodate) to standing water (Wolff, 2001).

1-3-7: Assessment and monitoring of IDD:

Monitoring of IDD prevention and control programs is crucial whether they are based on fortification or supplementation in order to ensure that additional iodine intake is effective in reducing the deficiency while preventing excessive intake that may lead to adverse health consequences. The monitoring process should include the assessment of coverage and iodine nutrition status. It is necessary to provide adequate dietary iodine to prevent brain damage in the fetus and in the young infant when the brain is growing rapidly. Measurements of salt and urinary iodine thereby provide the essential elements for monitoring whether IDD is being successfully eliminated. In order to be effective, the surveillance system needs (WHO, 2000):

(i) Laboratories for measurement of salt iodine and urinary iodine.

(ii) Production quality assurance charts and databases at the country level, for recording the results of the regular monitoring procedures, particularly for salt iodine, urinary iodine, thyroid size and, when available, neonatal TSH.

1-3-7-1: Urinary iodine excretion:

Iodide is well absorbed from the intestine, is distributed like chloride in the body and is rapidly excreted by the kidney (Bennett and Brown, 2003). The most sensitive method for evaluation of IDD control program is the determination of urinary iodine excretion. This is due to the effective clearance of this element by the kidneys regardless of other confounding factors. According to (Cecil and Plum, 1996) and (Dunn

and Van Derharr, 1990) the measurement of urinary iodine is a good and reliable index of dietary iodine intake.

The urinary iodine excretion in a casual sample is a valuable index for evaluating the iodine supply of population. The population sample size should be at least 50 – 100 because this number, statistically, allows for change in urinary iodine concentration arising from possible difference in dilution (Bourdox, 1986).

It is not practical to gather a 24-hour sample. Therefore, for evaluation surveys, it is recommended to get a random sample. Study of all age groups is practically not easy, yet as regards of susceptibility of children to the complication; they are studied as representatives of the society showing the iodine sufficient/deficiency status (Cecil and Plum, 1996).

A content of iodine in urine is normally used as a marker for status assessment of iodine deficiency disorder (IDD). The following values are guide for IDD status: <20µg/I (severe); 20-49µg/I (moderate); 50-100µg/I (mild) and >100 µg/I (normal) (Japan, analytical chemistry, 2001).

1-3-7-2: Thyroid size:

Thyroid size is sensitive marker for iodine deficiency because goitre, is the most severe consequence of iodine deficiency, is the most clinically evident (Benmiloud, *et al*, 1994). Examination of thyroid gland (goitre) by procedure according to criteria endorsed by the World Health Organization (WHO) & International Council for the Control of Iodine Deficiency Disorder (ICCIDD). Classification of goitre size in this system is as follows:

1- Grade 0: no goitre

2- Grade 1A: thyroid lobes larger than ends of thumbs.

Grade 1B: thyroid enlarged, visible with head titled back.

3- Grade2: thyroid enlarged, visible with neck in normal position.

4 – Grade 3: thyroid greatly enlarged, visible from 10 meters.

Grade 2 and grade 3 are collectively called visible goitre. WHO, UNICEF and ICCIDD, have proposed a modification of this system; combine grade 1A, 1B together, and grade 2 and 3 into second grade. However, this proposed classification may hinder the impact of IDD control programmes when goitres reduce in size from grade 1B to grade 1A or from grade 3 to grade 2 (WHO, UNICEF & ICCIDD,1993).

1-3-7-3: Other tests:

(i) Serum thyroglobulin concentration: is a sensitive measure of thyroid activity and hyperplasia. In iodine deficient infants and children, serum thyroglobulin concentration is high more than serum TSH. Although a nonspecific test, since any type of thyroid stimulation or injury raises the serum thyroglobulin concentration, the values correlate well with the severity of iodine deficiency (Benmiloud, *et al*, 1994).

(ii) ***Thyroid radioiodine uptake:*** is increased in iodine deficiency, because of both thyroid stimulation and the low iodine pool size, but is not a practical field test. Iodine uptake is used as an index of thyroid function, that can be easily measured by using trace doses of radioactive isotopes of iodine that have no known deleterious effect on the thyroid (Ganong, 1995). Radioactive iodine has a dangerous aspect as well since excessive exposure, such as from

nuclear fallout, is a major risk factor for thyroid cancer. This is especially true in infant and adolescent, whose thyroid cells are still actively dividing (Murry,*et al*,1993).

1-4: Previous studies

1-4-1: In Sudan:

Eltom *et al* (1984) have surveyed the prevalence of goitre in Darfur area in Western Sudan. They found that goitre is highly endemic and the overall prevalence of goitre in the population was 85% (Eltom,*et al*,1984).

Osman and Fatah (1980) suggested that the causes of goitre are not only related to iodine deficiency. Contents of drinking water (high sodium, potassium and iron), low vitamin A intake and high consumption of millet are another factors (Osman and Fatah,1981).

Elnagar *et al* (1995) conducted study in Soja in western Sudan to evaluate the effect of different doses of iodized oil on goitre size. They reported that oral administration of 200 mg iodine is effective and acceptable for treating iodine deficiency in adult for one year (Elnagar,*et al*,1995).

Abdel Rahim (2005) had conducted study to estimate the incidence and degree of goitre in basic schoolchildren in Kosti, Rabak and Jebel Awlia and the effect of iodine deficiency on thyroid function. His study showed that these areas had high incidence of goitre due to iodine deficiency (Abed Rahim,2005).

1997 survey of 7 zones gave the following median UI, in mcg/L: Darfur, 20; Upper Nile, 40; Kordofan, 48; Central, 70; Northern, 90; Khartoum, 96; Eastern, 98. A 2000 survey of 984 children in the south

showed median UI of 100 mcg/L. Several goitre prevalence surveys conducted by the Government identified regions at high risk of IDD, including Darfur state (TGR = 87%), central region (TGR = 78%) and other regions with moderate goitre levels; Khartoum (TGR = 17%) and Port Sudan (TGR = 13%). Research study on water iodization in Kurdufan and Nuba Mountains found baseline TGR 69%, UI 15-20 mcg/L (IDD newsletter,2001).

Elnour A, *et al,* (2000). Had conducted study to investigated deficiencies of iodine, iron, and vitamin A and their possible interaction in preschool children in the southern Blue Nile area of Sudan. Their results indicate that goitre is endemic in this region of Sudan despite iodine sufficiency and that both anemia and vitamin A deficiency are health problems in the area. Moreover, consumption of millet, vitamin A deficiency, and protein-energy malnutrition are possible etiologic factors in this endemic area.

Elnagar, *et al* (1997). Were examined the technique of measuring thyroid-stimulating hormone (TSH) on filter paper blood samples for use in evaluating the iodine nutrition status of newborns and adults living in iodine-deficient areas. Filter paper blood samples were obtained between the 5th and 7th day after birth from 103, 43 and 103 term newborns living in Khartoum (mild iodine deficiency), Kosti (moderate iodine deficiency) and Darfur (severe iodine deficiency), respectively. TSH was measured with a commercial assay and the levels were compared with those obtained with the same method in 1147 samples from term Swedish newborns, obtained on the 3rd to the 5th

day of life. The mean TSH for all three Sudanese groups was higher than the Swedish mean ($p < 0.001$).

Bani (2007). Adduced paper uses a public health approach to examine briefly: the progress of universal salt iodisation (USI) in Sudan; (b) the roles of the main factors involved; and (c) the main issues around accelerating USI. In Sudan the prevalence of goitre is 22 per cent. It is assumed that productivity among the people affected is reduced by 5–25 per cent. Little apparent progress has been made with USI. The Government of Sudan, UN multilateral agencies, international consultative groups, bilateral agencies, global and national non-governmental organizations and, increasingly, the private sector must work together to find innovative approaches to increase awareness of the broader social, public health and nutritional contexts, and to advocate for increased national and international funding.

1-4-2: In EMR:

El sayed *et al* (1991) conducted study to assess the prevalence of IDD among Cairo schoolchildren and concluded that IDD is mildly severe in Cairo governorate .The highest prevalence of goitre was in the north Cairo (27.51%) and the lowest was in central Cairo (6.59%). Grade 1B goitre was more prevalent than 1A (Elsayed,*et al*,1991).

In 1993 study on goitre conducted in Morocco by Aquaron and found that the median value of urinary iodine in endemic areas was 1.8 µg /dl and 2.4 µg /dl for cases and controls respectively (Aquaron,1993).

Roudsari,*et al* (2001) conducted study to assessment IDD in Iran. Most cases (52.19%) showed urine iodine concentration between 10 – 30 µg /dl. As well 5.85 % of pupils, had mild iodine deficiency according to world standard, 1.45% of pupils showed moderate and none had severe IDD.

1-4-3: In the world:

Wyss *et al* (1996) conducted a nationwide sample survey in Chad to establish the prevalence of iodine deficiency disorders (IDD). 1171 people between 10 and 20 years of age were included in the survey. The overall weighted prevalence of goitre, evaluated by a clinical examination was 63%. (Wyss,*et al*,1996).

Rasmussen LB.(2008) conducted study to assess an iodine fortification programmes in Denmark. The study was reported that the change in urinary iodine excretion caused by fortification. Intake of milk and salt had strong significant direct associations with iodine excretion. The authors concluded that although the median iodine intake in the whole study population is at the recommended level, some groups still have a low intake and it is important to have a moderate milk intake to obtain a sufficient iodine intake in Denmark (Rasmussen,2008).

Lucatero A. (2008) conducted a cross-sectional study to determine the prevalence of iodine deficiency, its causes and its association with intelligence quotient (IQ). His study was done of thyroid size, urinary iodine excretion, IQ, and other variables in schoolchildren (n=303) in Colima, Mexico. Overall goitre rate was

21.4%; low urinary iodine excretion was found in 19.5% of the children, high urinary iodine excretion in 32.0%. 92% of the population used iodized salt, but a deficient iodine level was found in 86.8% of salt samples. Moderate iodine deficiency was associated ($P < 0.05$) with a 4.26 times higher risk of low IQ (Lacatero,2008).

Gastseva and Argirova were conducted a cross-sectional study included schoolchildren between the ages of 11 and 14 years from 2 villages in Bulgaria with high and low nitrate levels in drinking water. The comparison between the median urinary iodine levels of the total number of exposed and nonexposed children showed statistically significant differences. The results of the study confirmed the role of high nitrate levels in drinking water as a health risk factor for thyroid dysfunction (Gastseva and Argirva,2005).

Mukhopadhya S. *et al* were applied experiments on rats. Rats were fed diet containing 3% potassium nitrate (KNO3) for 4 weeks and then thyroid gland weight, urinary iodine excretion pattern, thyroid peroxidase (TPO) activity, serum levels of total thyroxin (T_4), triiodothyronine (T_3) and thyroid stimulating hormone (TSH) concentrations were evaluated for thyroid status. In nitrate treated animals, the weight of thyroid gland was increased significantly ($P<0.001$) while thyroid peroxidase activity ($P<0.01$), serum T_4 ($P<0.01$) and serum T_3 levels ($P<0.001$) were reduced; but serum TSH level was increased ($P<0.001$) along with slightly elevated iodine excretion level ($P<0.001$) in comparison to control animals. The overall results indicated the development of a relative state of functional

hypothyroidism with enlarged thyroid after nitrate exposure. (Mukhopadhya,*et al*,2005).

In the early 1920s Goldemberg, working in Argentina showed that fluoride was displacing iodine; thus compounding the damage and rendering the community hypothyroid from iodine deficiency. In the 1930s of May, Litzka used fluoride preparations to treat over active thyroid illness. Their patients either drank fluoridated water, swallowed fluoride pills or were bathed in fluoridated bath water; and their thyroid function was as a result, greatly depressed (Goldemberg and semana, 1921 & Litzka, 1937).

Van Maanen *et al.* (1994) studied the effect of nitrate contamination of drinking water on volume and function of the thyroid in human populations exposed to different nitrate ion levels in their drinking water. No iodine deficiency was observed in any of the nitrate exposure group. A dose-dependent difference in the volume of the thyroid was observed between low and medium versus high-nitrate exposure groups, showing development of hypertrophy at nitrate levels exceeding 50 mg/l. An inverse relationship was established between the volume of the thyroid and serum thyroid stimulating hormone (TSH) levels. These effects are supported by similar findings in rats and pigs (Van Maanen,*et al*,1994).

Clark *et al*. in 1960 conducted study to use of iodinated poppy seed oil in the prevention of endemic goitre. They found that injection of 2ml (950 mg iodine) iodinated poppy seed oil (lipidol) had

demonstratable effects on thyroid function lasting as long as 2 years (Clarke.*et al,*1960).

Balabolkin *et al*. (1995) studied the thyroid and immune status in workers continuously exposed to fluorine. T_3 is seen reduced in 51% of the workers. The examinees with 'euthyroid condition' had immune disorders with an allergic tendency. In workers with subclinical hypothyroidism, the immune alterations were more evident, T-lymphocytes count rose, but their functional activity declined, indicating impaired cooperation of immunocytes as a result of imperfect control under low concentrations of T_3 (Balabolkin,*et al,*1995).

Sakamoto, *et al* (2001). The effects of green tea extract catechins on the rat thyroid were examined in a 13 week feeding study and subsequent 2, 4 and 8week studies. Commercially available polyphenon-60 (P-60) which contains green tea extract catechins at 66.2% was used as a source of catechins. In the 13 week study, 10 rats of each sex were administered diets containing P-60 at 0 (control), 0.625, 1.25, 2.5 and 5.0%. Goitres were observed in the 13-week test. The mean thyroid weight of rats fed a diet containing 5.0% of P-60 (5.0% group) significantly increased to 444% of the control in males and to 304% of the control in females. These results indicate that dietary administration of the green tea extract catechins at high doses induced goitres in rats, and this may be due to antithyroid effects of catechins. (Sakamoto, *et al*, 2001)

2-1: Subjects

2-1-1: Study Nature:

Cross sectional community and hospital based study.

2-1-2: study Area:

This study has been conducted in Shendi province that extends alongside the Nile River in the Southern part of Nile River State to the North of Khartoum on the eastern verge of the Nile. The majority of populations are belonging to Eljaalein tribe. The main food is Wheat and Dura, the source of water is an artesian wells.

2-1-3: Study Community:

This study was conducted in period from October to December 2007 on two separate communities:

a. Basic schools' children (6 – 9 years) in the centre of Shendi city.

b. Patients who present to the hospital with thyroid symptoms.

2-1-4: Sample selection:

Random sampling technique was used. Shendi town was divided into four geographical zones: north, south, east, and west. From each zone two schools (boys& girls) were selected. From the two hospitals in Shendi city, any patient presented with thyroid disorder during the study period was incorporated in the study.

2-2: Study Methods

2-2-1: Questionnaire:

Include questions about sex, age, residence, school performance, source of water supply and iodized salt consumption among Shendi population.

2-2-2: Clinical assessment (Goitre survey):

A team of doctors and laboratory technicians helped in clinical assessment of the study sample children and in obtaining urine specimens from a randomly selected subgroup of them. Examination of the thyroid gland was by palpation procedure according to criteria endorsed by the World Health Organization (WHO) and International Council for the Control of Iodine Deficiency Disorder (ICCIDD).

Classification of goitre size in this system is as follows:

(i) 0 : No goitre.

(ii) 1A : Thyroid lobes larger than ends of thumbs.

1B : Thyroid enlarged, visible with head titled back.

(iii) 2 : Thyroid enlarged, visible with neck in normal position.

(iv) 3 : Thyroid greatly enlarged, visible from 10 meters.

"2 and 3 are collectively called visible goitre" (ICCIDD, *et al*, 1990)

2-2-3: Laboratory investigations:

2-2-3-1: Iodine concentration in urine:-

Sample:

Three hundred and fifty three children were selected randomly to determined urinary iodine concentration. To each urine sample a few drops of formalin were added and then kept refrigerated until were delivered to the laboratory after one week.

Test Principle:-

The urine is digested in strong acid at high temperature; thereafter the color change of ammonium sulfate with another substance (arsenic acid) is accelerated by iodine as catalyzing agent. The speed of the change in color depends on the iodine concentration. Measurement of the color intensity and the iodine content, comparing to standard solution with known iodine content was performed with colorimeter. This reaction, which is called the Sandell-Kolthoff reaction (1973), has been diagramed as follows:

$$2Ce^{+4} + 2I^{-} \longrightarrow 2Ce^{+3} + I_2$$

$$I_2 + As^{+3} \longrightarrow As^{+5} + 2I^{-}$$

The ceric ion has a yellow colour, while the cerous is colorless (karmarker *et al*. 1986)

Equipments:

1- Heating block.
2- Colorimeter.
3- Vented fume hood with perchloric acid trap.
4- Thermometer.
5- Test tubes (13mm × 100mm).
6- Reagent flasks and bottles.
7- Pipettes.
8- Laboratory balance.

Reagents:

1- Potassium chlorate ($KClO_3$).

2- Perchloric acid ($HClO_4$).

3- Arsenic trioxide (AsO_3).

4- Sodium chloride (Na Cl).

5- Sulfuric acid (H_2SO_4).

6- Ceric ammonium sulfate ($Ce\ (NH_4)_4\ (SO_4)_4\ .\ 2H_2O$).

7- Deionized water (H_2O).

8- Potassium iodate (KlO_3).

From the previous reagents the following solutions were prepared:

1- Chloric acid solution.

2- Arsenious acid sulfate solution.

3- Ceric ammonium sulfate solution.

4- Standard iodine solution.

Procedure: -

Each urine samples was firstly shacked evenly to even distribution of any suspension. From each urine sample a 250µ1 was pipetted into a 13×100 mm test tube. Blank (250µ1of water) was prepared in 13×100 mm test tube. A set of iodine standard at concentrated (2, 5, 10 and 15 µg/dl) were also prepared (250µ1 for each tube). To each tube of the sample, blank and standards chloric acid solution was added (750 µl), then mixed gently and heated for 50 – 60 minutes in a heating block at 115 C^0. After cooling to room temperature about 3.5 ml of arsenious acid solution was added to each tube, and mixed by inversion and kept for 15 minutes at the same temperature. Ceric ammonium sulfate (350 µ1) was added quickly to each tube and mixed well using vortex. The

absorbance at 450 nm for each sample was measured using colorimeter after 20 minutes of additional of ceric ammonium sulfate.

Calculation:

A standard curve was draw by plotting iodine concentration of each standard against its absorbance reading. Iodine concentration for each sample was determined in g/dl from standard curve, using the sample absorbance.

Iodine in urine is normally used as a marker for status assessment of iodine deficiency disorder (IDD). The following values are guide for IDD status: < 2µg/dl severe; 2 - 4.9 µg/dl moderate; 5-10 µg/dl mild and >10 µg/dl normal (WHO, 2001 and analytical chemistry, Japan 2001).

2-2-3-2: Thyroid function test:-

Serum thyroid hormones and TSH concentrations were measured by inzymetic method using in commercial *Human Gesellschaft* method.

(i) T_3 test (competitive EIA):

Test principle:

The T_3 ELISA will be based on the principle of competitive binding between T_3 in a test specimen and T3- peroxidase conjugate for a limited number of binding sites on the anti T_3 (sheep) coated well. Thus the amount of T_3 peroxidase conjugate bound to the well is inversely proportional to the concentration T_3 in the specimen. After incubation of specimen and T_3 – peroxidase conjugate unbound enzyme conjugate is removed in the equilibrium state by washing. TMB, substrate solution, is added and blue colour develops. The intensity of

this colour, which changes to yellow after stopping the reaction, is inversely proportional to the amount of T_3 in the specimen.

The absorbance of calibrators and specimen is determined by using ELISA microtiter reader with the wavelength set at 450 nm or by automated ELISA system. Specimen concentration is extrapolated from a dose response curve generated by utilizing serum calibrators of known antigen concentration.

Reagents and Contents :-

(1) 12 Microtiter strips (MIC)

8-well snap-off strips , coated with anti- T_3 (sheep)

(2) A - F Calibrators (CAL)

T_3 level : A:0, B:0.5 , C: 1.0, D: 2.5,E: 5.0, and F: 7.5 ng/dl

(3) Enzyme – antigèn conjugate (CON)

(4) Conjugate buffer (C –DIL)

(5) Wash solution (WS)

(6) Substrate reagent A (SA) 3,3',5,5', tertamethylbenzidine (TMB)

(7) Substrate Reagent B (SB)

(8) Stop solution (STOP) (Sulphuric acid)

(9) 1 Adhesive strip.

Reagent preparation :-

All reagents was brought to room temperature (15 - 25 C°) before use .

(1) ***Working conjugate solution (WCON)***

CON 1 +10 was diluted with C-DIL: e.g.

160µl CON with 1.6 ml C-DIL for 16 wells.

(2) ***Working wash solution (WASH)***

WS was diluted to 1000 ml with fresh, deionised water in a suitable container with rinsing the vial several times.

(3) ***Substrate working solution (SUB)***

For use within 30 days, Content of the vial SA was poured in vial SB then mixed and stored at 2 - 8C°.

Specimen

Patient's serum

Wash procedure:

Automatic washer was used, prime with WASH and strip was washed 3 times. The washer fills all wells completely and aspirate off efficiently after 30 sec. After washing remaining liquid was removed by tapping the plate upside down on tissue paper.

Procedure:- Reagents and specimens were at room temperature.

Step 1	Calibrators µl	Specimens µl
a- CAL A- F; in duplicate	50	-
b- Specimen	-	50
c- WCON	100	100
d- was mixed and cover MIC with adhesive strip		
f-was incubated 60 min at 20 – 25 C^o		
e- wash 3 times.	300	300

Step 2	Calibrators	Specimens
a-SUB	100	100
b- Incubated 15 min at 20 - 25 C^o		
c- STOP	50	50
d- Mixed carefully		
The absorbance was measured at 450 nm as soon as possible.		

Calculation: -

A dose response curve was used to interpolate the concentration of T_3 in unknown specimen. The best - fit curve was drawn through the plotted points from CAL absorbance versus the corresponding T_3 concentration ng/dl for on linear graph paper. To determine the concentration of the T_3 for unknown sample (s), the average absorbance of the duplicates were located on the vertical axis of the graph , the intersecting point was found on the curve , and the concentration (in ng/dl for T_3) from the horizontal axis of the graph.

(ii) T_4 test (competitive EIA):

Test principle:

The T_4 ELISA will be based on the principle of competitive binding between T_4 in a test specimen and T_4- peroxidase conjugate for a limited number of binding sites on the anti T_4 (sheep) coated well. Thus the amount of T_4 peroxidase conjugate bound to the well is inversely proportional to the concentration T_4 in the specimen. After incubation of specimen and T_4– peroxidase conjugate unbound enzyme conjugate is removed in the equilibrium state by washing. TMB, substrate solution, is added and blue colour develops. The intensity of this colour, which changes to yellow after stopping the reaction, is inversely proportional to the amount of T_4 in the specimen.

The absorbance of calibrators and specimen is determined by using ELISA microtiter reader with the wavelength set at 450 nm or by automated ELISA system. Specimen concentration is extrapolated from

a dose response curve generated by utilizing serum calibrators of known antigen concentration.

Reagents and Contents:-

(1) 12 Microtiter strips (MIC)

8-well snap-off strips, coated with anti- T_4 (sheep)

(2) A - F Calibrators (CAL)

T_4 level: A: 0, B: 2.0, C: 5.0, D: 10.0, E: 15.0, and F: 25 µg/dl

(3) Enzyme – antigène conjugate (CON)

(4) Conjugate buffer (C –DIL)

(5) Wash solution (WS)

(6) Substrate reagent A (SA) (TMB)

(7) Substrate Reagent B (SB)

(8) Stop solution (STOP)

(9) 1 Adhesive strip

Reagent preparation:-

All reagents was brought to room temperature (15 - 25 C°) before use . Reagents not in use should always be stored at 2 - 8 C°.

(1) ***Working conjugate solution (WCON)***

CON 1 +10 was diluted with C-DIL : eg

160µl CON with 1.6 ml C-DIL for 16 wells.

(2) ***Working wash solution (WASH)***

WS was diluted to 1000 ml with fresh, deionised water in a suitable container with rinsing the vial several times.

(3) ***Substrate working solution (SUB).***

For use within 30 days, content of the vial SA was poured in vial SB then mixed and stored at 2 - 8C°.

Specimen

Patient's serum

Wash procedure:

Automatic washer was used, prime with WASH and strip was washed 3 times. The washer fills all wells completely and aspirate off efficiently after 30 seconds. After washing remaining liquid was removed by tapping the plate upside down on tissue paper.

Procedure:-

Reagents and specimens were at room temperature.

Step 1	Calibrators µl	Specimens µl
a- CAL A- F; in duplicate	25	-
b- specimen	-	25
c- WCON	100	100
d- was mixed and cover MIC with adhesive strip		
f- was incubated 60 min at 20 – 25 C^o		
e- Wash 3 times.	300	300

Step 2	Calibrators	Specimens
a-SUB	100	100
b- Incubated 15 min at 20 - 25 C^o		
c- STOP	50	50
d- Mixed carefully		
The absorbance was measured at 450 nm as soon as possible.		

Ca

Calculation: -

A dose response curve was used to interpolate the concentration of T_3 in unknown specimen. The best - fit curve was drawn through the plotted points from CAL absorbance versus the corresponding T_3 concentration ng/dl for on linear graph paper. To determine the concentration of the T_3 for unknown sample (s), the average absorbance of the duplicates were located on the vertical axis of the graph , the intersecting point was found on the curve , and the concentration (in ng/dl for T_3) from the horizontal axis of the graph.

(iii) TSH test (Sandwich EIA):-

Test principle:

The TSH ELISA is based on classical sandwich ELISA technique. As a second generation assay, it makes use of a highly specific monoclonal anti TSH antibody coated on the surface of the microtiter wells. In the first incubation step, specimens, calibrators or controls and enzyme conjugate (peroxidase-labelled anti-TSH) are mixed to form the sandwich complex which is bound to the surface of the wells by the interaction with immobilized antibody. At the end of incubation, excess enzyme conjugate is washed out. Substrate reagent is added and the resulting colour, which turns into yellow after stopping the reaction with the stop solution, is measured photometrically. The absorbance increase is directly proportional to the TSH concentration and is evaluated by means of a calibration curve that is established from the calibrators supplied with the kit.

Reagent and contents:-

1- Microtiter strip (MIC)

8 Well snap-off strip, coated with anti – TSH.

2- Calibrators (CAL)

A , B , C, D , E , & F ,TSH level : 0 , 0.5 , 3.0 , 6.0 , 15 , & 30.0 ml U/l respectively.

3- Enzyme conjugate (CON)

Anti-TSH (goat) ,HRP- labeled

4- Wash solution (WS)

5- Substrate reagent (SUB): (TMB)

6- Stop solution (STOP) 15ml

7- Adhesive strip (1)

Reagent preparation:-

All the reagents were bringing to room temperature (15 – 25 C^o) before were used.

Working wash solution WASH

WS was diluted 1 + 20 with fresh deionised water, e.g. 50 ml WS + 1000 ml = 1050 ml.

Specimen:

Patient's serum

Wash procedure:-

i- Automatic washer was used, prime with WASH and strip was washed 3 times. The washer fills all wells completely and aspirate off efficiently after 30 sec.

ii- After washing , remaining liquid was removed by tapping the plate upside down on tissue paper.

Procedure: -

Reagent and specimens were at room temperature.

Step 1	Calibrators µl	Specimens µl
a- CAL A- F; in duplicate	50	-
b- specimen	-	50
c- WCON	100	100
d- was mixed and cover MIC with adhesive strip		
f- was incubated 60 min at 20 – 25 C^o		
e- Wash 3 times.	300	300

Step 2	Calibrators	Specimens
a-SUB	100	100
b- Incubated 15 min at 20 - 25 C^o		
c- STOP	50	50
d- Mixed carefully		
The absorbance was measured at 450 nm as soon as possible.		

Calculation:-

(1) CAL- Plot the absorbance for each duplicate versus the corresponding TSH concentration in ml U /l on linear graph paper.

(2) The best - fit curve was drew through the plotted points

(3) To determine the concentration of the TSH for unknown sample (s) , the average absorbance of the duplicates was located on the vertical axis of the graph , the intersecting point was found on the curve , and was read the concentration (ml U /l) from the horizontal axis of the graph .

2-3-3-3: Water samples analysis:

Samples of water source from study area were analyzed in the Water Department, National Center Laboratories, Federal Health Ministry, Sudan. The analyses were done under the following general dissections:

(i) Fluoride (Alizarin visual method):

Test principle:

This method is based on the reaction between fluoride and a zirconium-dye lake. Fluoride reacts with the dye lake, dissociating a portion of it into a colorless complex anion $(ZrF_6)^{2-}$ and the dye. As the amount of fluoride increase, the color produced becomes progressively lighter or of different hue. Because this method is subject to error due to interfering ions, it may be necessary to distill the sample before making the colorimetric determination. However, in many instances natural drinking water does not contain these interfering ions in excess of the tolerances of the method, and hence the fluoride determination may be made directly without distillation. Turbidity may be removed with filtration. Colored water, water with alkalinity in excess of 400mg/l as $CaCO_3$, and water with sulfate content greater than 300 mg/l should be distilled before colorimetric determination.

Apparatus:-

Color comparison equipment, Nessler tubes, matched, 100 ml, tall form

Reagents:-

(i) ***Stock fluoride solution*****:** 0.2210mg anhydrous sodium fluoride was dissolved in distilled water and diluted to 1000 ml;1.0 ml =100 µg F^-.

Standard fluoride solution: 10ml stock fluoride solution was diluted to 100 ml with distilled water; 1.0 ml = 10.0 µg F^- .

(ii) ***Zirconyl-alizarin reagent:*** 0.3 g zirconyl chloride octhydrate ($ZrOC_{12}.8H_2O$) was dissolved in in 50 ml distilled water contained 1 L glass-stopped volumetric flask. 0.07 g 3-alizarinsulfonic acid sodium salt (alizarin red S) dissolved in 50 ml distilled water and was poured slowly into the zirconyl solution while stirring.

(iii) ***Mixed acid solution:*** 101 ml con. HCl was diluted to approximately 400 ml with distilled water. Carefully, 33.3 ml conc. H_2SO_4 was added to approximately 400 ml distilled water. After cooling, the two acids were mixed.

(iv) ***Acid-zirconyl-alizarin reagent*****:** To the clear zirconyl-alizarin reagent acid solution was added mixed in the 1 L volumetric flask. Distilled water was added to the mark and mixed. The reagent was changed from red to yellow within an hour and was then ready to use.

Procedure:-

A series of standard were prepared by taking the following volumes of standard fluoride solution (10 µg /ml) and was diluting to 0.0, 1.0, 2.0, 3.0, 4.0 and 5.0 ml. The temperature of standards and samples was adjusted so that deviation among them was no more than 2 C^0. To 100 ml clear samples acid-zirconyl-alizarin reagent were added. Mixed thoroughly and samples and standard were compared after 1 hour.

Calculation:

$$F^- /l\ (mg) = (A/ml\ sample) \times (B/C)$$

Where: A= µg F-dependent visually

B/C: dilution factor.

<u>(ii) Nitrate (Cadmium reduction method):</u>

Test principle:

Nitrate (NO_3^-) is reduced almost quantitatively to nitrite (NO_2^-) in the presence of cadmium. The nitrite produced thus is determined

calorimetrically. A correction may be made for any nitrite present in the sample by analyzing without reduction step.

Apparatus:-

(i) Reduction column

(ii) Calorimetric equipment; spectrophotometer for se at 543 nm

Reagents:

(i) ***Nitrate-free water:*** distilled water was used; absorbance of blank not exceeds 0.***01.***

(ii) ***Copper-cadmium granules:*** 20 gm (5-20 mesh Cd granules) was washed with 6N HCl and was rinsed with water. Cd was swirling with 100 ml 2% $CuSO_4$ solution until blue color partially was faded (5 minutes). With fresh $CuSO_4$ was decanted and repeated until a brown colloidal precipitate was developed. Gently, the precipitated Cu was removed with water.

(iii) ***Color reagent:*** 10 ml 85% phosphoric acid and 1.0 gm sulfanilamide was added to 80 ml water. Magnetically stirred to dissolve sulfanilamide completely, 0.1 gm N-(1-naphthyl)-ethylenediamine dihydrochloric acid was added. Mixed to dissolved, and then was diluted to 100 ml with water.

(iv) ***Ammonium chloride-EDTA solution:*** 13 gm ammonium chloride and 1.7 gm EDTA were dissolved in 900 ml water. Ph was adjusted to 8.5 with conc. NH_4OH and diluted to 1L.

(v) ***Hydrochloric, 6N***

(vi) ***Copper sulfate solution 2%:*** 10 gm $CuSO_4.5H_2O$ was dissolved in 250 ml water and diluted to 1L.

(vii) ***Stock nitrate solution:*** potassium nitrate was dried in an oven at 105 ^0C for 24 h.0.7218 g was dissolved in water and diluted to 1000 ml; 1.0ml = 100 µg NO_3^- N. Preserved with 2 ml $CHCl_3$.

(viii) ***Stock nitrate solution:*** 0.62 g Na NO_2 was dissolved in water and diluted to 500 ml; 1.00ml = 250 µg N. preserved with 1 ml $CHCl_3$.

Procedure:

A glass wool plug was inserted into bottom of the column and filled with water. Sufficient Cu-Cd granules were added to produce a column 20 cm long. Column was washed with 200 ml 1:1 NH_4Cl – EDTA solution. Column a activated by passing through it, at about 10 ml /min, 100 ml of a solution composed of 100 ml 1.0 mg NO_3 –N /L and 10 ml NH_4Cl –EDTA solution. A suitable volume of sample was taken (1.0 ml to 50 ml) in 100 ml volumetric flask. 10 ml NH_4Cl –EDTA solution was added, made to volume with water and mixed. Mixed sample was poured into column and collected at a rate of about 10 ml / min. 50 ml was discarded first and the rest was collected. Cu-Cd column was washed and stored in 1:1 NH_4Cl –EDTA solution if was not to be used for several hours. A suitable volume reduced sample was taken (2.0 – 25.0ml) in 50 ml volumetric flask 2.0 ml color reagent was added, completed to volume and mixed. Between 10 min and 2 hour afterward, absorbance was measured at 543 nm against water reagent blank. The stock nitrate was used to prepared standards; 0.0, 1.0, 2.0, 3.0 and 4.0 mg NO_3^{-}“ –N. at least one NO_2^- standard was compared to a reduced NO_3^- standard at the same concentration to verify reduction column efficiency.

Calculation:

Standard curve was obtained by plotting absorbance of standards against NO_3^-–N concentration. Compute sample concentration directly from standard curve. Report as NO_3^- mg N/L

Alkalinity (titration method):

Test principle

Hydroxyl ions present in a sample as a result of dissociation or hydrolysis of solutes react with addition of standard acid. Alkalinity thus depends on the end-point pH used. Phenolphthalein alkalinity is an alkalinity measured by titration to pH 8.3. Total alkalinity is a term used for the quantity measured by titration to PH about 4.5.

Apparatus:-

i- Titration vessel: conioal flask 250 ml and abeaker 400 ml.

ii- Magnetic stirrer.

iii- Pipettes, volumetric.

iv- Burettes.

Reagents:-

i- ***Sodium carbonate solution, 0.025 M:*** about 3 g analytical reagent Na_2CO_3 was dried at 250^0C for 4h and cooled in a desiccator. 2.65g was dissolved in water and transferred to 1-L volumetric flask; flask was filled to mark with water.

ii- ***Standard hydrochloric acid, 0.1M:*** 8.5 to 9.0 ml conc.HCL was diluted to 1-L standardize against 40.0 ml 0.025M $N_{a2}C_{O3}$ solution, with about 60 ml water, in a beaker by titrating potentiometrically to pH of about 5. Lidded out electrodes, rinsed in the same beaker, and boil gently for 3 to 5 min under a watch glass cover. After cool to room temp. Cover glass was rinsed into beaker, and finish titrating to the pH inflection point. Calculate molarity.

$$\text{Molarity, M} = \frac{A \times B \times 2}{C}$$

A: Molarity of Na_2CO_3 solution.

B: ml Na_2CO_3 solution taken.

C: ml acid used.

iii- Methyl orange indicator solution.

iv- Phenolphthalein solution, alcoholic.

Procedure:

100 ml of sample was discharged with a pipette into conical flask. 3 drops of phenolphthalein indicator was added. Titration was done over white surface to the end point. To the same sample 3 methyl orange was added and titrated to the medium-orange color end point.

Calculation:

$$\text{Phenolphthalein alkalinity, } CaCO_3 \text{ mg/l} = \frac{A \times B \times 50000}{C}$$

Where:

A: Molarity of acid (HCl)

B: ml acid used; phenolphthalein end point

C: Volume of sample taken

$$\text{Total alkalinity, } CaCO_3 \text{ mg /l} = \frac{A \times B \times 50000}{C}$$

Where:

A: Molarity of acid (HCl)

B: ml acid used; methyl orange end point

C: Volume of sample taken

2-3-4: Statistical Analysis:

The data were collected and Statistical analysis was cured out using SPSS programme. Mean, variance, standard deviation and other

parameters were calculated for comparison between different groups. The confidence limit was 95% and 99%, the P value was considered significant at values 0.05 and 0.01 respectively.

3: RESULTS

3-1: Sample distribution:-

A sample of 1214 pupil (593 male and 621 females) was randomly selected to represent the four study areas and was subjected for clinical examination of thyroid disorders.

According to geographical zones of the study area 27.8% of the sample were from eastern Shendi and 20.1% were from southern Shendi, representing highest and lowest percentages respectively and this is shown in (Figure 3-1).

It is quite clear when the study sample was distributed according to sex and study zones, that the females were predominant in the four areas and formed 51.2% of the total sample. This represented in (Figure 3-2).

3-2: Goitre incidence:-

The incidence of goitre among Shendi schoolchildren was shown to be 14.6%) of the total sample as indicted by (Figure 3-3).

According to goitre grades it is observed that grade 3 goitre was not detected in the study sample. Grade 2 goitre was recorded only in 2.8%, grade 1A in 75.2% and grade 1B in 22.0% of goitrous cases in study sample and this is clearly evident in (Figure 3-4).

The distribution of goitrous cases in the study sample according to sex showed that the highest incidence was in females (15.8%) as compared to males (13.3%) with no statistically significant difference ($p = 0.216$) and this is represented in (Figure 3-5).

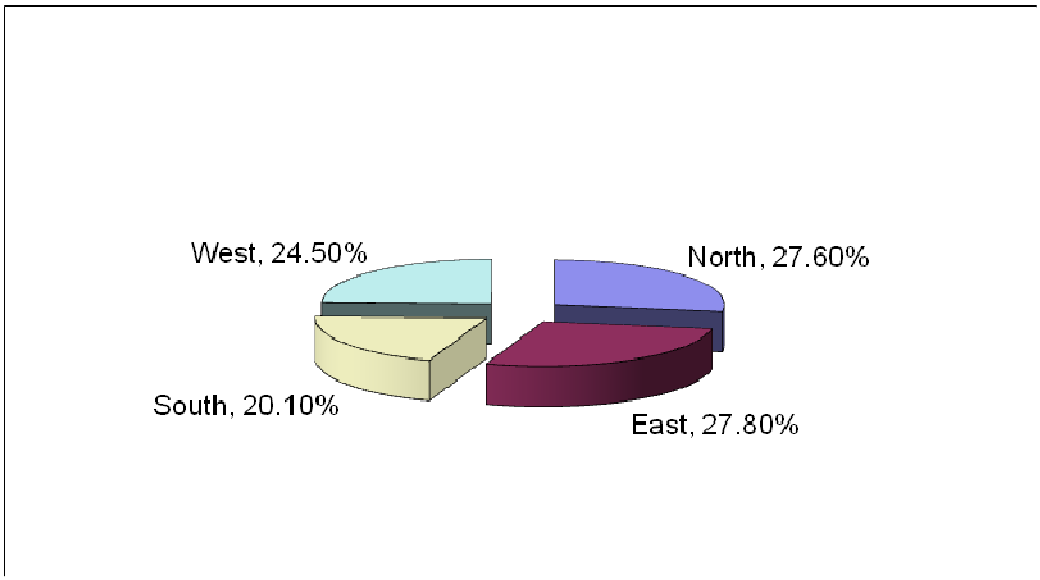

Figure (3-1) sample distribution according to children residence.

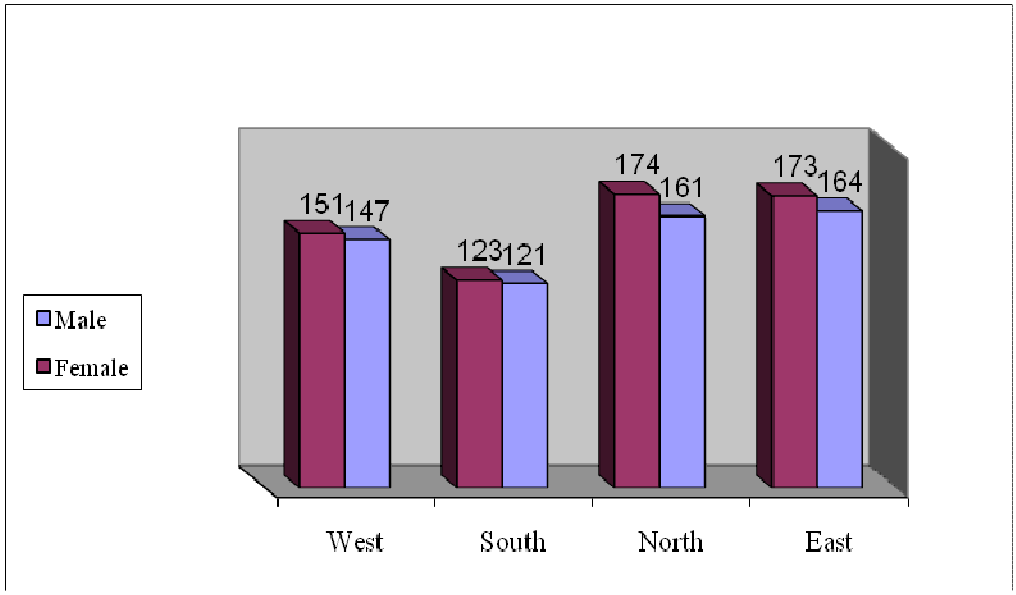

Figure (3-2) sample distribution according to sex.

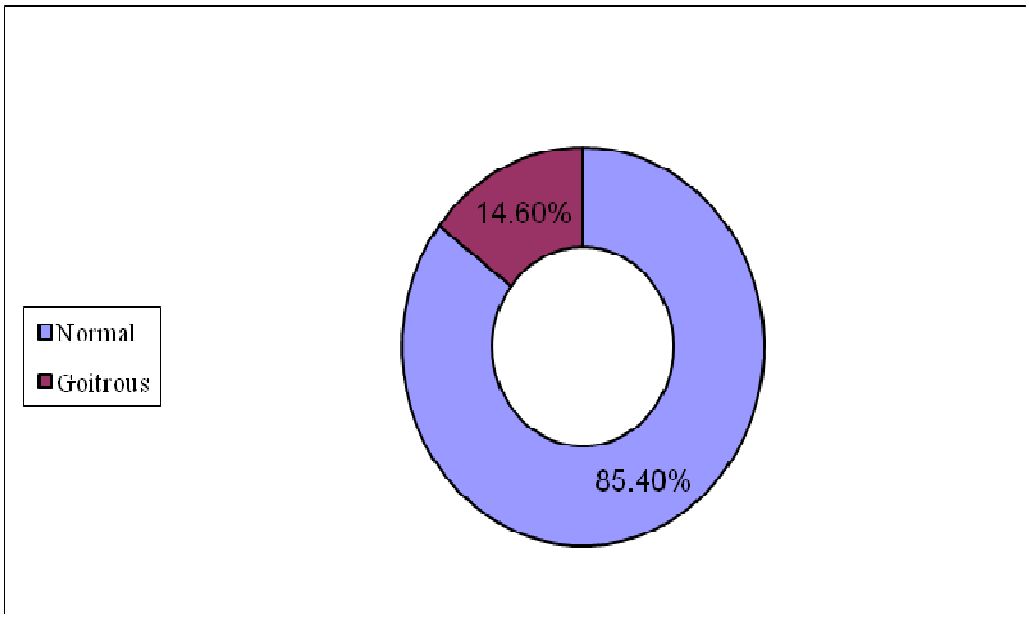

Figure (3-3) the incidence of goitre in study area.

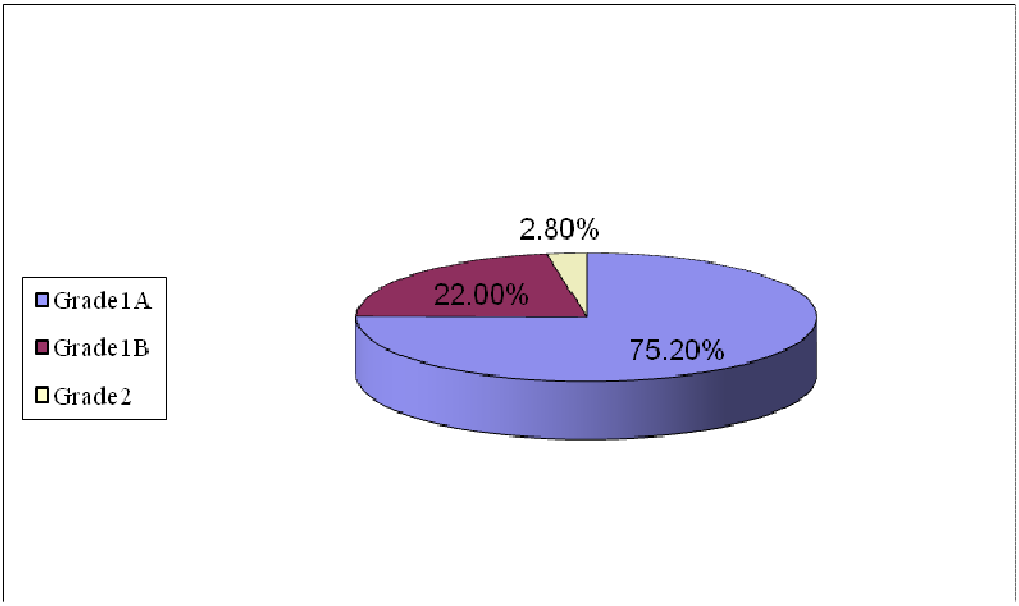

Figure (3-4) the goitre grade incidence

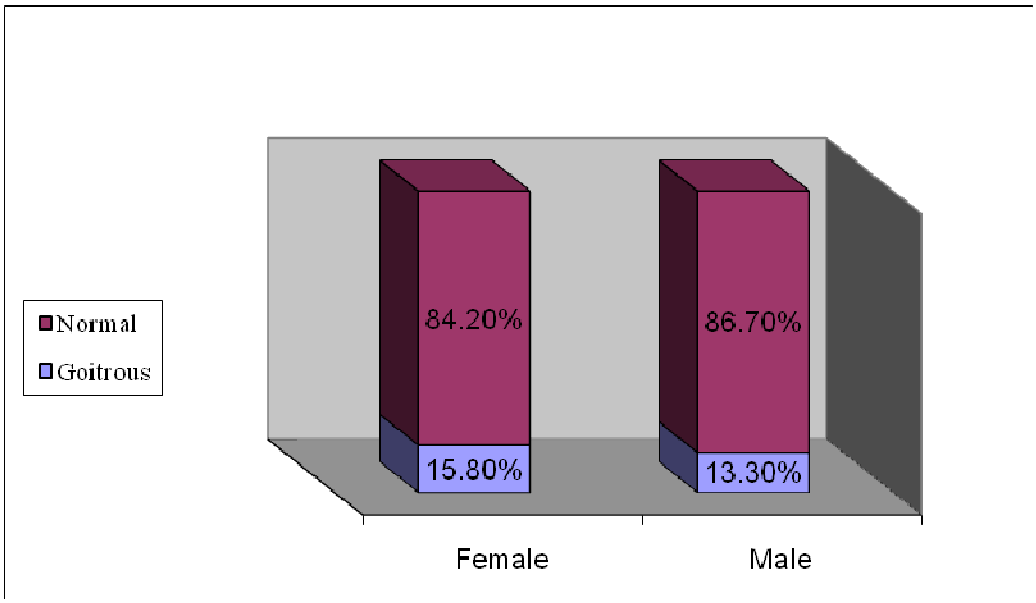

Figure (3-5) the incidence of goitre according to sex

By distribution of goitre according to the geographical zones and sex among Shendi schoolchildren examined, it is quite clear that the highest incidence was in southern Shendi (23.4%) and the lowest was in eastern Shendi (11.3%). Goitre was found to be more common in females than in males except in west area where it is more in males (12.2%) in contrast to females (11.3%). The difference in goitre prevalence for zones was statistically significant ($p<0.05$). This is illustrated in (Figure 3-6).

The distribution of goitrous cases among Shendi schoolchildren examined with reference to age. The incidence was found to be increasing with age. It was lowest (11.0%) at 6 years and highest (16.0%) at 9 years. The difference in goitre incidence per age was statistically not significant ($p = 0.093$) and this is clearly evident in (Figure 3-7).

3-3: School performance:-

The school performance of goitrous children in study sample is observed that the highest percentage 53.7% of goitrous children was in the low level of intelligence and the lowest percentage 8.0% was in the level of extremely intelligence. In this study, children school performance was determined by referring to their school degrees and teachers' observations (extremely intelligence > 80, high intelligence 60 – 70, moderate intelligence 50 – 60 and low intelligence < 50). This is illustrated in (Figure 3-8).

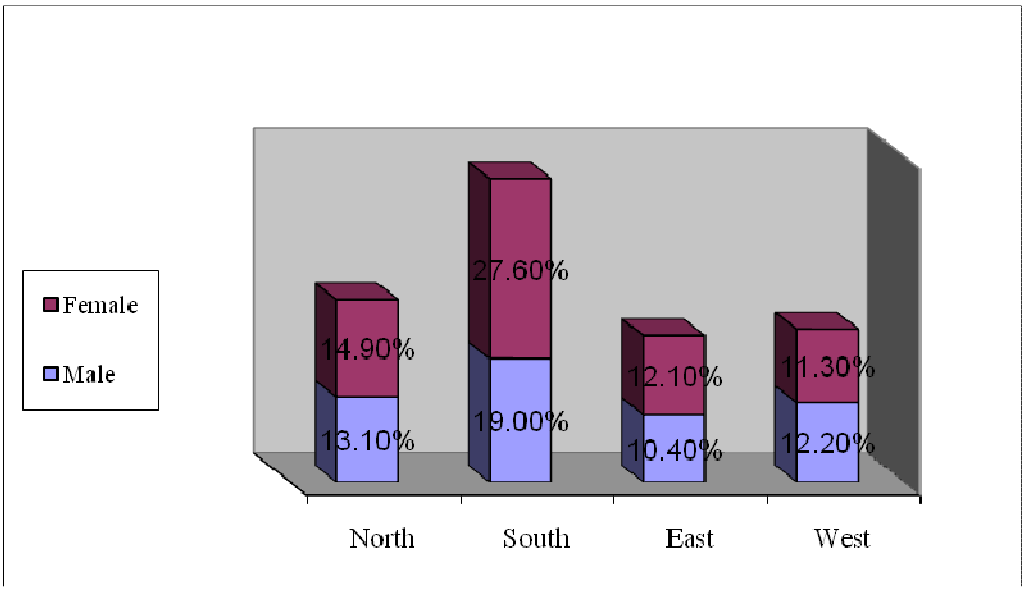

Figure (3-6) the incidence of goitre according to zones and sex.

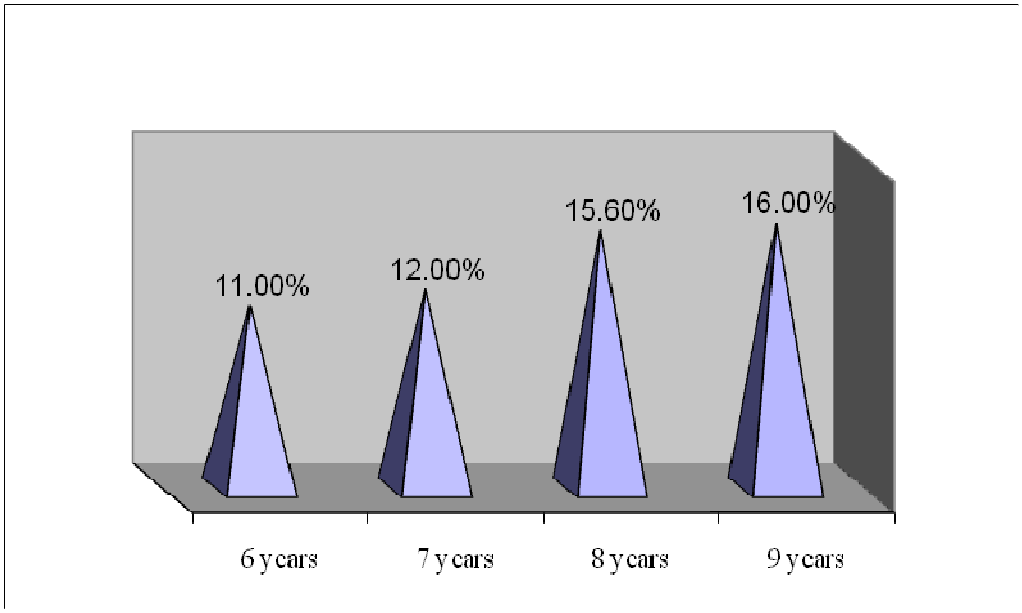

Figure (3-6) the incidence of goitre with reference to age

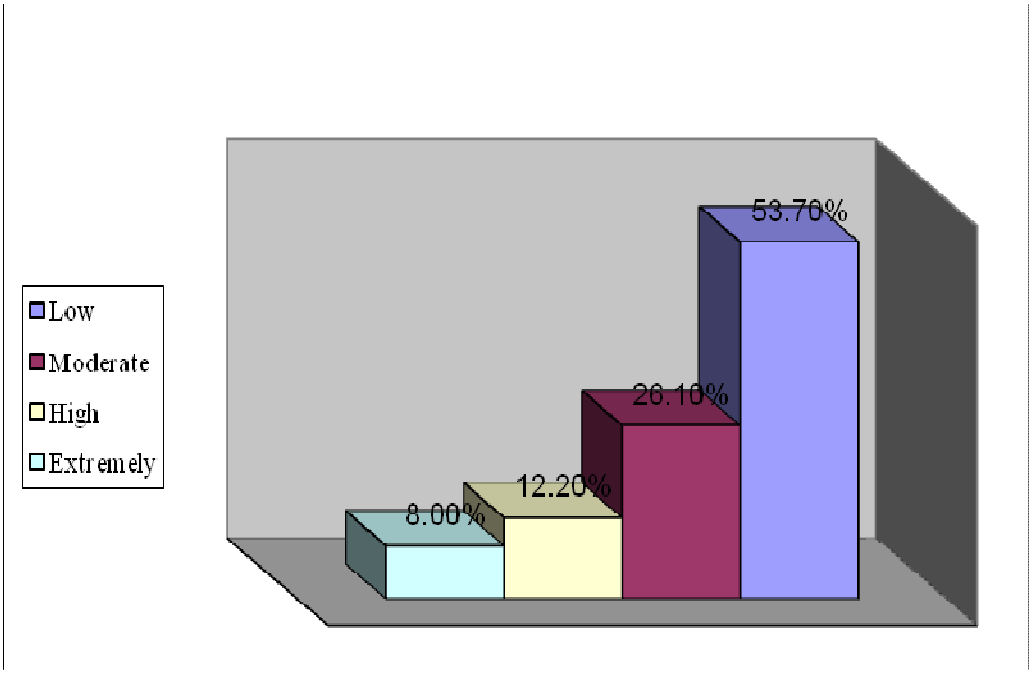

Figure (3-8) the school performance of goitrous children.

3-4: Urinary iodine excretion:

A sample of 353 schoolchildren was selected for assessment of urinary iodine concentration from four regions (north, east, south and west) in Shendi city. The latest WHO standards were utilized to demonstrate the whole sample iodine status. According to this criteria there was 2.6% of cases had severe iodine deficiency (<2µg/dl). Moderate (2 - 4.9µg/dl) and mild (5 - 10µg/dl) iodine deficiency were found in 4.5% and 16.4% of the study sample respectively. There for 68.6% of the study sample was found to have urinary iodine concentration of 10 - 30 µg/dl which is normal and 7.9% to have concentration of >30µg/dl, this is represented in (Figure 3-9).

Urinary iodine excretion in schoolchildren of the four geographical zones it is evident that most cases had a urine iodine concentration of (10 - 30µg/dl) which is normal and this is clearly evident in (Figure 3-10).

The mean urinary iodine excretion of children in the four study zones it showed that the difference between four groups was statistically significant ($p< 0.005$) this is clearly evident in table (3-1).

The mean urinary iodine excretion according to sex it showed that females had higher values than males. The difference in mean urinary iodine excretion per sex was statistically significant ($p < 0.01$) and this is shown in (Table 3- 2).

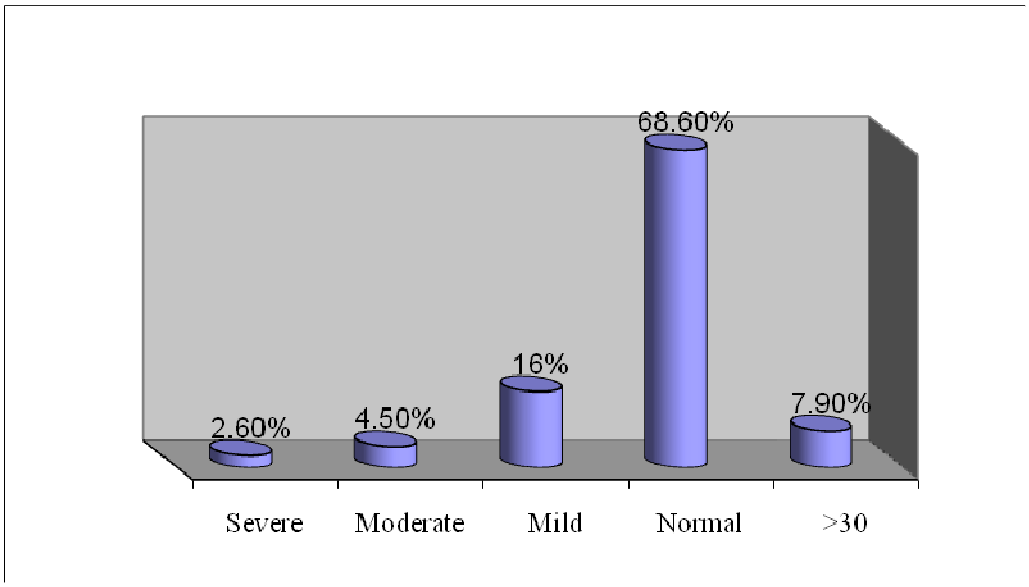

Figure (3-9) the urinary iodine concentration according to WHO scales.

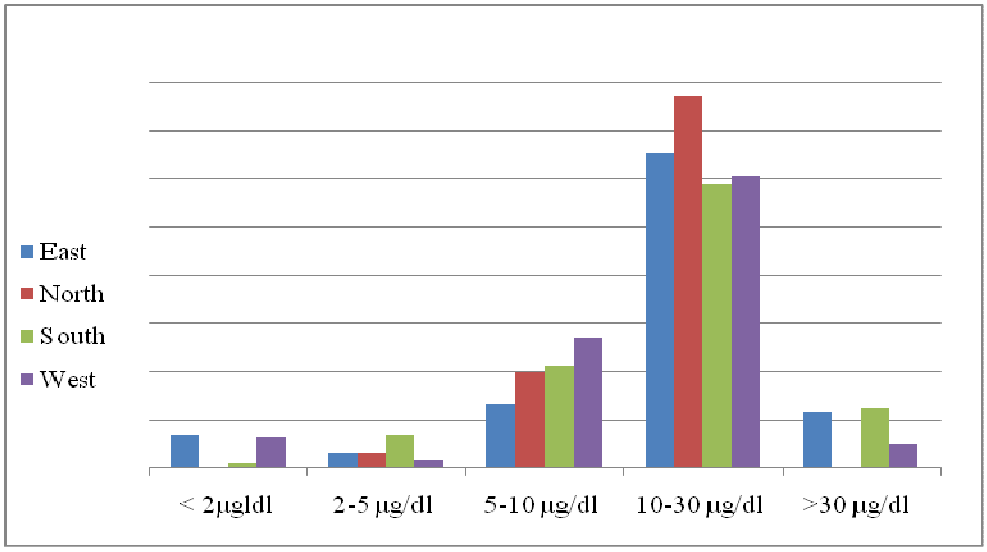

Figure (3-10) the urinary iodine concentration in schoolchildren according to zones.

Zone	*N*	*Mean*	*Standard deviation*
North	96	13.86	3.88
South	74	17.43	11.93
West	85	14.46	11.23
East	98	23.40	30.64
Total	353	18.42	20.62

Table (3-1) the mean and standard deviation of urinary iodine excretion of children in four study zones.

Sex	*N*	*Mean*	*Standard deviation*
Males	171	15.49	10.88
Females	182	21.16	26.45

Table (3-3) the mean and standard deviation of urinary iodine excretion according to sex.

The urinary iodine excretion between both sexes it is showed that 26.9% of females were suffering from iodine deficiency, 10.8% of them had severe iodine deficiency, 19.3% of them had moderate iodine deficiency and 69.9% of them had mild iodine deficiency. While 19.9% of males suffering from iodine deficiency, 8.8% of them had severe iodine deficiency, 20.6% of them had moderate iodine deficiency and 70.6% had mild iodine deficiency. Generally, 23.5% of children had urinary iodine excretion less than normal (< 10 µg / dl) according to WHO criteria, 18.9%, 19.3% and 69.9% of them had severe, moderate and mild iodine deficiency respectively. This is clearly evident in (Table 3-4).

The mean and standard deviation of urinary iodine excretion of children in the four study zones according to age. It is quite clear that there was apparent correlation between urinary iodine excretion and age progress. The difference per age was statistically significant ($p < 0.05$) and this is represented in (Table 3-4).

3-5: Foodstuffs:-

Foodstuffs those argued a positive correlation with children iodine status, either iodine intake or urinary iodine excretion. Milk is one of which consumed daily (91.7%) and millet is rarely consumed in study area (19.9%) this is indicated in (Table 3-5).

3-6: Thyroid function test:

136 hospital patients who presented to the Shendi hospitals during the study period with goitre, most of them were females (86.0%) and this is illustrated in (Figure 3-11).

Sex	Severe (< 2 µg/dl) %	Moderate (2 – 4.9 µg/dl) %	Mild (5 - 10 µg/dl) %	Normal (10 - 30 µg/dl) %	> 30 µg/dl %
Male (171)	1.8	4.1	14.0	74.3	5.8
Female (182)	3.2	4.9	18.7	63.3	9.9
Total (353)	2.5	4.5	16.4	68.7	7.9

Table (3-3) the urinary iodine concentration according to WHO scales between both sexes.

Age	*N*	*Mean*	*Standard deviation*
6 years	93	22.61	27.55
7 years	89	20.09	19.05
8 years	86	17.42	20.75
9 years	85	13.62	11.02

Table (3-4) the mean and standard deviation reference with age.

Foodstuff	*Iodine intake*	*Iodine excretion*
Milk	P< 0.005	N.C
Eggs	P< 0.001	N.C
Fish	P< 0.001	N.C
Peanuts	N.C	P< 0.001
Maize	N.C	P< 0.001
Millet	N.C	P< 0.005

Table (3-5) the co-relation between foodstuffs consumed in the study area and children iodine status. (N.C: No correlation)

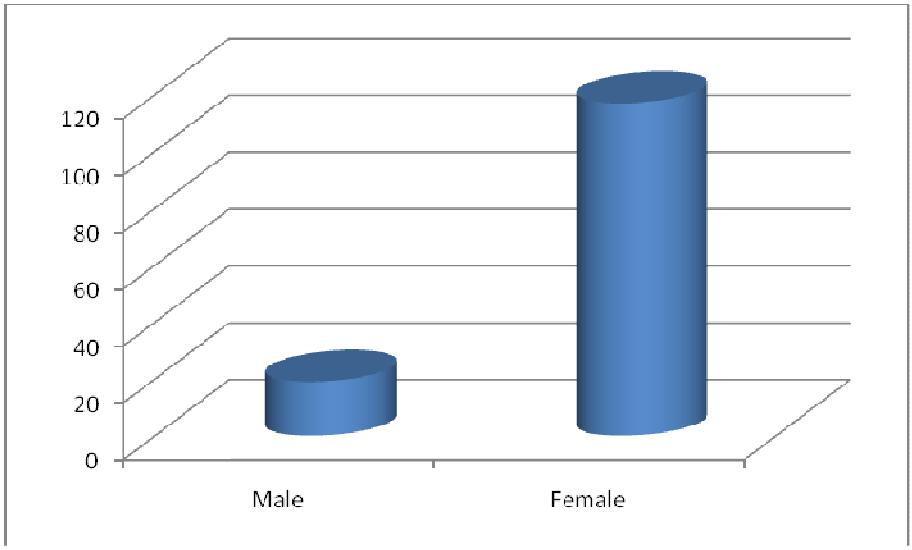

Figure (3-12) the distribution of hospital patients according to sex.

Hospital patients were subjected to thyroid function test so T_3, T_4 and TSH were assessed. The thyroid function test for patients, most of them (61.0%) were euthyroids, 26.5% were hyperthyroids and 12.5% were hypothyroids and this is clearly evident in (Figure 3-12).

The thyroid hormones (T_4 and T_3) and TSH were respectively (8.7 ± 3.34 µg/dl), (1.5 ± 1.27 ng/ml) and (3.3 ± 4.53 mlU/l) for euthyroids; (13.4 ± 3.41µg/dl), (3.3 ± 2.00 ng/ml) and (0.16 ± 0.20 mlU/l) for hyperthyroids and (2.6 ± 1.57 µg/dl), (0.7 ± 0.90 ng/dl) and (24.4 ± 26.33 mlU/l) for hypothyroids this is represented in (Table 3-6).

3-7: Water samples:-

Some minerals and anions in water samples from four study areas were known affect the iodine metabolism and may take place in the prevalence of goitre in Shendi area. The minerals concentrations were distributed in an approximate ratio in the four-study areas this is showed in (Table 3-7).

3-8: Iodized salt consumption:

The knowledge and consumption of iodized salt among randomly selected group in Shendi city. It is observed that most of the sample (77.5%) did not know what the iodized salt is and only 4.1% were using it as a table salt and this is showed in (Table 3-8).

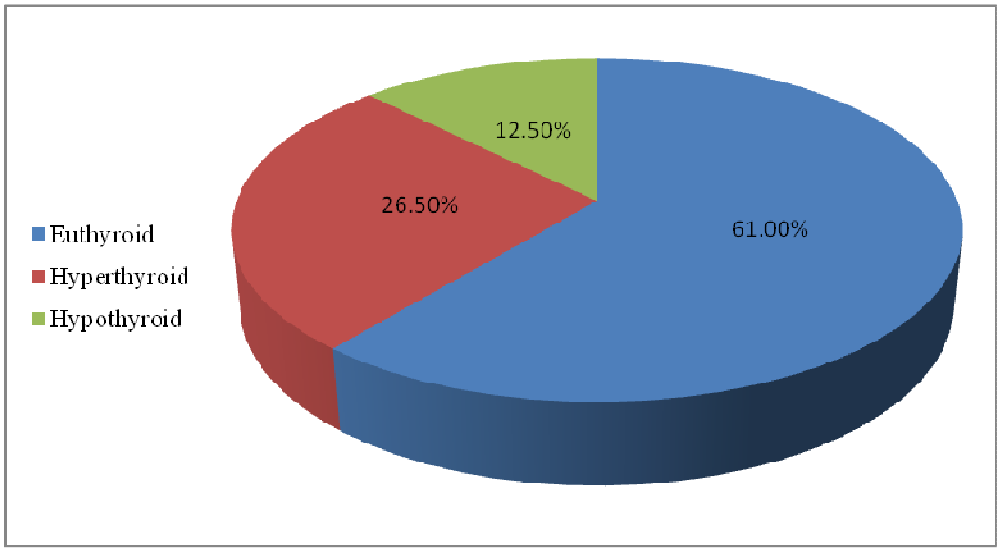

Figure (3-12) the thyroid function test of hospital patients.

Condition	***Euthyroid***			***Hyperthyroidism***			***Hypothyroidism***		
Hormone	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH
Mean	8.7	1.5	3.3	13.4	3.3	0.16	2.6	0.7	24.4
S.D.	3.34	1.27	4.53	3.41	2.00	0.20	1.57	0.90	26.33
No.	83			36			17		

Table (3-6) the mean and standard deviation of thyroid hormones and TSH of hospital patients.

Water source(region) / *Minerals*	*North*	*East*	*West*	*South*
Fluoride *(mg/l)*	0.15	0.35	0.35	0.15
Nitrate *(mg/l)*	3	3.0	3.0	3.0
$CaCO_3$ *(mg/l)*	160	160	160	160
Calcium *(mg/l)*	30	36	34	30

Table (3-7) the concentration of some minerals and anions that affect the iodine metabolism in water samples from four study area.

Education level	*Do you know iodized salt*		*Do you use it*	
	Yes (%)	**No (%)**	**Yes (%)**	**No (%)**
Illiterate	0.0	100	0.0%	100
General education	10.9	89.1	1.8	98.2
Graduate and post graduate	90.3	9.7	16.1	83.9

Table (3-8) the iodized salt consumption in study area.

4: DISCUSSION

4-1: The selection:

Medical observation of presence of many cases of goitre and thyroid disorders in Shendi hospitals, encourage us to conduct study in this city to understand the effect of iodine deficiency in school performance, incidence of goitre among the school children and patient with thyroid symptoms. In addition, Shendi is my home and I hope to see it in excellent healthy situation.

Samples were selected randomly from for zones; east, north, west and south of Shendi in order to determine the incidence of iodine deficiency. Schoolchildren from four zones (1214 pupils) were subjected to study goitre incidence. However 353 of schoolchildren were selected for the study the urinary iodine excretion. Selection of sample based on the distribution of Shendi population.

4-2: Goitre incidence:

Goitre size in the study area was determined by WHO and ICCIDD procedure, in which goitre size is classified as follows:

1- Grade 0: No goitre.

2- Grade IA: Thyroid lobes larger than ends of thumbs.

IB: Thyroid enlarged, visible with head titled back.

3- Grade II: Thyroid enlarged, visible with neck in normal position.

4- Grade III: Thyroid greatly enlarged, visible from 10 meters.

Goitre was recorded in 14.6% of the total sample, affecting both sexes, with incidence of 13.3% in males and 15.8% in females. According to regional distribution, the highest incidence was recorded in

southern Shendi (23.4%), while the lowest was in eastern Shendi (11.3%).

From (Figure 3-4) 75.2% of cases had grade 1A, 22.0% of cases had grade 1B, 2.8% of cases had grade 2 and no cases showing grade 3 were detected. From these percentage 53.4%, 64.1% and 60.0% were found to be females respectively. Goitre incidence was found direct proportionally with age. It was highest (16.0%) at 9 years and lowest at 6 years (Figure 3-7).

In Shendi rate goitre incidence rate among schoolchildren (14.6%) was found to be higher than that reported by Abdou *et al*. (13.5%), in port Sudan city. On other hand, rate of goitre incidence among schoolchildren was lower than those reported by Eltom (Darfur) and Abdel Rahim (Kosti Rabak and Jebel Awlia areas) which were (85%) and (53%) respectively.

4-3: Children school performance:

Iodine deficiency has apparent effect on the intellectuality of schoolchildren; it reduced the intelligence degree. Mild iodine deficiency reduced the intelligence quotients (I.Q) by 10 - 15 % (Marberly.*et al*, 1994). By using the children school performance and teachers' observations, the result of our study showed that most of goitrous cases at low level of intelligence degree (53.7%), and small group of them with excellent degree (8.0%) (Figure 3-8).

4-4: Urinary iodine excretion:

The most sensitive method for evaluation of IDD control program is the determination of urinary iodine excretion, due to the effective

clearance of this element by the kidneys. In this study, the grades of urinary iodine excretion depend on the WHO classification: < 2.0 µg/dl (severe); 2.0 - 4.9 µg/dl (moderate); 5.0 -1 0.0 µg/dl (mild) and 10.0 - 30 µg/dl (normal).

The total mean of urinary excretion is (18.42 ± 20.62). The large standard deviation indicates the large difference in values of urinary iodine excretion in studied schoolchildren samples. Generally, the females showed higher concentration of urine iodine excretion (21.16 µg/dl) than that of males (15.45 µg/dl). However according to WHO classification 63.2% of females had normal urinary iodine excretion (10-30µg/dl), 26.9% of females were suffering from iodine deficiency (<10 µg/dl) and the rest of female (9.9%) had urinary iodine excretion more than 30 µg/dl. From (Table 3-3) the females suffering from iodine deficiency were 3.2% severe, 4.9% moderate and 18.7% mild. While 74.3% of males had normal level of urinary iodine excretion(10 -30 µg/dl), 19.9% of males suffering from iodine deficiency (< 10 µg/dl), and the rest (5.8%) had urinary iodine excretion more than 30 µg/dl. 1.8% of males had severe urinary iodine excretion (< 2 µg/dl), 4.8% had moderate urinary iodine excretion (2 – 4.9 µg/dl) and 14.0 % had mild urinary iodine excretion (5 – 10 µg/dl). Generally, according to WHO criteria, 23.5% of children had urinary iodine excretion less than normal (< 10 µg/dl) 18.9%, 19.3% and 69.9% of them had severe, moderate and mild iodine deficiency respectively (Table 3-3).

Urinary iodine excretion was found to be reversely proportional to schoolchildren age in Shendi city. Schoolchildren at 9 years of age showed the lowest urinary iodine excretion (13.62 µg/dl) while those at 6 years of age showed the highest urinary iodine excretion (22.61 µg/dl).

The difference per age in urinary iodine excretion was statistically significant ($p< 0.05$) (Table 3-4)

The study revealed that the majority of highest levels (> 50 µg/dl) of urinary iodine excretion were observed to be in southern and eastern regions. These observations could explain the highest mean values of urinary iodine excretion for schoolchildren from eastern (23.4 µg/dl) and southern (17.4 µg/dl) regions of Shendi city.

3-5: Foodstuffs:

From questionnaire analysis of goitrous children foodstuffs were showed a positive correlation with children iodine status, regarding both the iodine intake and urinary iodine excretion. Eggs, fish and milk appeared to be correlated with iodine intake (Table 3-5). The correlation was strong for milk ($p < 0.005$) and very strong for the first egg and fish ($p < 0.001$). This could be explained by the mean of urinary excretion of the study samples (18.42µg/dl) which was found to be within the normal range according to WHO criteria. Peanuts, maize and millet were found to be correlated with urinary iodine excretion showing very strong correlation ($p < 0.001$) with the Peanuts, maize items and was strong for the millet ($p < 0.005$) ; maize (Volpe,1998), millet (Sartelet, *et al*,1996), and peanuts (NHIC,2005) might have a goitrogenic effects on the iodine status of children in the study area according. This is reflected in the highest urinary iodine excretion reported in south and east regions which showed the highest consumption of these items.

Four factors; foodstuffs, age, sex and area zone were clearly obtained from this study to affect the goitre incidence and urinary iodine excretion. There was a highly significant difference between both sexes

for urinary iodine excretion ($p < 0.01$). There was also significant difference between the four regions for goitre incidence ($p < 0.05$).This significance in such a small geographical area (Shendi) may indicate the implication of other cofactor than iodine deficiency in this goitrogenesis. This is substantiated by higher rates of iodine excretion in eastern Shendi especially among females schoolchildren (more than 100 µg/dl) , and this might be probably due to higher consumption of goitrogens, which may lead to appearance of symptoms of iodine deficiency, and sequences which explain the high incidence of goitre among female than males.

4-6: Thyroid function test:

Interpretation of T_3 and T_4 levels depends on knowledge of the TSH value. In the euthyroid state, T, T_4 and TSH levels will all be within normal range. Florid thyroid failure causes T_3 and T_4 depression and elevation of the TSH. Incipient or developing thyroid failure is characterized by low normal values of the T_3 and T_4 and elevation of the TSH. In toxic states the TSH level is suppressed and undetectable (Mann, *et al*, 1995).

Analysis of the result for thyroid function test done for patients with goitre in Shendi hospitals during the study period showed that (61%) were euthyroid, (24.5%) were hyperthyroids and (12.5%) were hypothyroids (Figure 3-12), with reference normal ranges of the kits used for TSH, T_3 and T_4 as described in the Material and method.

From (Table 3-6) the mean values for TSH, T_3 and T_4 for patients in Sheni were found to (3.3 ± 4.53 mlU/l), (1.5 ± 1.27 ng/ml) and (8.7 ± 3.34 µg/dl), respectively for euthyroids; (0.16 ± 0.2 mlU/l), (3.3 ± 2.00

ng/ml) and (13.4 ± 3.41 µg/dl) respectively for hyperthyroids and (24.4 ± 26.33 mlU/l), (0.7 ± 0.90 ng/ml) and (2.6 ± 1.57 µg/dl) respectively for those who were hypothyroids.

The high percentage of euthyroids in the studied population reflected the normal or near normal iodine levels, may be due to compensation of the iodine deficiency by the gland. Decrease in the thyroid hormones production lead to increase TSH production, which lead to compensatory hyperplasia of the thyroid gland resulting in hormone levels becoming normal with enlargement of the gland (Danish, 2005). This euthyroidism is not exclusively iodine dependent as many factors as medications may have a role.

In the group of hypothyroidism, which might be due to iodine deficiency as main cause, a marked reduction can be observed in T_4 (2.6 ± 1.57 µg/dl) (Table 3-6), which is the main hormone secreted by the thyroid gland. Despite the deficiency state in the hypothyroidism, the T_3 level showed mild reduction (lower limit of normal range) and this might explain the metabolism of T_4 and it's deiodination to T_3. Moreover, high TSH mean level (24.04mlU/l) can be observed due to continuous pituitary stimulation by lower levels of thyroid hormones (Danish, 2005). This high TSH level resulted in goitre development with no effect on thyroid hormones, may be due to iodine deficiency or any other internal cause as "Hashimoto's thyroiditis".

There was obvious difference in standard deviation of the TSH level among the three studied groups. It was high in euthyroid group, and this explains variable levels for stimulation of thyroid hormones. On the other hand the TSH standard deviation was low in hyperthyroid group, since inhibition of TSH secretion.

The high percentage of euthyroids group was correspondent with the results obtained from the analysis of urinary iodine excretion and clinical assessment where iodine was found in mild concentration and schoolchildren with categorized with grade A.

According to sex factor (Figure 3-11), most of affected patients were females (86%) and this means that thyroid disorders were spreading among females more than males and showed significant difference at $p < 0.001$ by using chi - square test.

4-7: Water sources:

In most cities, surface water is the main source of drinking water. Treatment and disinfection of this water are rather problematic. The analysis of drinking water of the study areas raveled it contained some goitrogenic minerals such as; fluoride nitrate magnesium, calcium and manganese (Table 3-7). In spite of low concentration of these minerals they have an effect on long time on schoolchildren to induce goitre. The obvious results was supported results done by (Goldemberg, 1921), (Geneva, 1974), (Gaur, *et al,* 1989) and (Van Koetsveld, 1964). Therefore, proper nutrition and a healthy water supply are crucial in the prevention and treatment of goitre.

The erroneous usage of toothpaste especially during childhood may take place in the increment of fluoride effect as goitrogenic mineral and consequent increase in goitre incidence.

En masse, the most cases of iodine deficiency had mild urinary iodine excretion, and there were few cases where urinary iodine excretion concentration was more than 30µg/dl. In brief we considered, the iodine deficiency in Shendi area at the mild deficiency level, and this

is due to the effect of goitrogenic and dietary iodine deficiency. This hypothesis (goitrogenic effect) can be supported by the fact that most of Shendi population use to eat foods containing iodine such as fish, eggs, yogurt, milk, onions, cheese, radishes and watercress at least once a week. Clinical examination of schoolchildren showed that high goitre rates were in females than in males, although they had significant elevation in their urinary iodine excretion than in males.

A goitrogenic food in study area includes maize, millet, tea and peanuts (NHIC, 2005), which is consumed mostly in a form of (dakwa). In addition the metabolism vegetable oils and animal fats increase the requirement of iodine (Kalkus, 1920). Drinking water also may participate in this effect, by its contamination of goitrogenic minerals especially fluoride and nitrate.

4-8: Iodized salt utilization:

One of the important solutions of goiter prevention is utilization of iodized salt. In spite of that high percent (95.9%) of Shendi people do not used the iodized salt and about 77.4% of them did not hear about it. The rezones for that is educational (Table 3-8).

According to International Council for the Control of Iodine Deficiency Disorder (ICCIDD,2008), Shendi city is categorized in group 4; in which less than 20% of the households have access to iodized salt. The authorities should assess the current situation of its salt iodization program in the town to identify the problems and to update its strategies and action plans.

5-1: CONCLUSION

1. The goitre incidence among Shendi basic school children was 14.6%; the female incidence (15.8%) was more than that of male (13.3%). Grade 1A goitre (75.2%) was more than others grades.
2. The high incidence of goitre was in the south Shendi (23.4%) and the lowest was in the east Shendi (11.3%). By age goitre incidence was highest at 9 years and lowest at age 6 years. Iodine deficiency had high effect on the schoolchildren performance, which was observed in most of goitrous cases (53.7%) with low intelligence level.
3. Most of schoolchildren (68.6%) had normal urinary iodine excretion, (10 - 30 µg/dl), 23.5% were suffering from iodine deficiency and 7.9% had urinary iodine excretion more 30 µg/dl. East Shendi showed the highest value (23.40µg/dl) and the lowest values were observed in north Shendi (13.86µg/dl).
4. Most (61.0%) of patients showed a euthyroid state which result from mild thyroid hormones deficiency due to dietary iodine deficiency. Females were more affected than male (86.0% and 14.0% respectively).
5. Some goitrogenic minerals and anions (such as F^- , Ca^{2+} and NO_3^-) were concentrated in the water sources of study area. Most of Shendi population did not consume the iodized salt.

5-2: RECOMMENDATIONS

Based on data obtained from the present study, the following recommendations are suggested:

- Health education of inhabitants in study area about the importance of iodinated salt usage.

- Application of iodinated salt programmers by health authorities.

- Reduction of frequent management of iodine-containing foodstuff such as milk, so as to preserve the iodine content.

- Attempts should be made to reduce the effect of goitrogenic minerals in water sources of study area.

- Identifying the goitrogenic-containing foodstuff and organizing their consumption.

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7: APPENDIX

7-1: Questionnaire

(i) Pupils:

1- Sample No. ……...

2- Sex …… ……...

3- Pupils age . …….

4- School name ……..

5- pupils zone …….

6- Pupils school performance ……

7- Teacher's observation …….

8- Teeth past use ……

9- Childe nutrition:

Item	**Daily**	**Weekly**	**Monthly**	**No**
Milk				
Eggs				
Yoghurt				
Cheese				
Fish				
Bread				
Maize				
Radishes				
Watercress				
Peanut				
Millet				
Iodized salt	Yes ( )		No ( )	

10- Goitre assess:

Grade 0		
Grade 1		
Grade 2		
Grade 3		

11-Urinary iodine concentration …… µg/dl

(ii) Patients:

Thyroid function test

T_3 concentration ……..... nmol/dl

T_4 concentration …….....nmol/dl

TSH concentration …….. ml U/l

(iii) Shendi population:

1- Do you know what the iodized salt? Yes ( ) No ( )

2- Do you use it? Yes ( ) No ( )

3- Education level. Illiterate ( ) General education ( )

Graduate or post graduate ( )

7-2: Abbreviations:

BAT : Brown Adipose Tissue.

CSF : Cerebrospinal Fluid.

DIT : Diiodo Tyrosine.

EMR : Eastern Mediterranean Region.

GH : Growth Hormone.

hCG : Chorionic Gonadotrphin.

ICCIDD: International Council for the Control of Iodine Deficiency Disorders

IDD : Iodine Deficiency Disorder.

I.Q : Intelligence Quotient.

LDL : Low-density Lipoprotein.

MEN : Multiple Endocrine Neoplasia.

MHC : Myosin Heavy Chain.

MIT : Monoiodo Tyrosine.

NIS : Sodium /Iodide Symporter.

PUT : Propyl Thiouracil.

T_3 : Triiodothyronine.

T_4 : Thyroxine.

TBG : Thyroxine-binding Globulin.

TBPA: Thyroxine-binding Prealbumin.

TGR: Total Goitre Rate.

TSH : Thyroid Stimulating Hormone.

TRH : Thyroid-releasing hormone.

TSI : Thyroid Stimulating Immune Globulin G (Ig G).

UNICF : United Nations Children's Fund.

USI: Universal Salt Iodization.

VIP : Vasoactive Intestinal Peptide.

WHO : World Health Organization.

7-3: Criteria:

7-3-1 *Goitre size:((ICCIDD, UNICEF& WHO, 1993*)

1- Grade 0: no goitre

2- Grade 1A: thyroid lobes larger than ends of thumb.

Grade 1B: thyroid enlarged, visible with head titled back.

3- Grade2: thyroid enlarged, visible with neck in normal position.

4 – Grade 3: thyroid greatly enlarged, visible from 10 meters.

7-3-2: *Urinary iodine excretion(WHO,2001)*

I- WHO,2001:

Severe: 0 - 2 µg/ dl

Moderate: 2 - 5 µg/ dl

Mild: 5 - 10 µg/ dl

Normal: 10 - 30 µg/ dl

More than 30 µg/ dl

II- Japan society for analytical chemistry (2001):

Severe < 20µg/I

Moderate 20-49µg/I

Mild 50-100µg/I

Normal >100 µg/I

7-3-2: *Thyroid hormones function test(Ganong,1995)*

I- ***Murry, et al, 1993***

TSH : Less than 10 µg/ ml

Free T_4 : (0.8 - 2.4 ng/ dl) or (10 - 30 p mol/ l)

Total T_4 : (5.0 - 12 µg/ dl) or (65 - 165 n mol /l)

T_3 (80 - 220 ng/dl) or (1.2 - 3.3 n mol/l)

II- ***Ganong, 1995***

T_4 : - Free : (0.002 µg/ dl or 2.0 ng/dl)

- Plasma level: (8.0 µg/ dl or 103 ng/dl)

T_3 : - Free: (0.3 ng/ dl)

- Plasma level: 0.15 µg/ dl or 2.3 n mol/ l)

TSH: plasma level : 2 mU/ml

III- ***Human Gesellschaft***

1- Thyroxine (T_4 µg/dl):-

	Male	Female
Mean	7.6	8.2
Standard deviation	1.6	1.7
Expected range	4.4 - 10.8	4.8 - 11.6

2- Triiodothyronie (T_3 ng/ml):

Mean	1.36
Standard deviation	0.33
Expected range	0.69 - 2.02

3- TSH (ml U/ l): 0.3 – 6.2