Thyroid Function in the Sick Thyroid Syndrome in Khartoum and El Shaab Teaching Hospitals, Khartoum- Sudan

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أليكَ يا آدم

(72) الآية

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To the soul of my mother.
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Finally, many thanks go to my father, brothers, sisters, friends and all who helped in the development and improvement of this study.
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACTCH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AMP</td>
<td>Adenosine mono phosphate</td>
</tr>
<tr>
<td>CCU</td>
<td>Cardiac Care Unit</td>
</tr>
<tr>
<td>D1</td>
<td>Type 1 deiodinase</td>
</tr>
<tr>
<td>D2</td>
<td>Type 2 deiodinase</td>
</tr>
<tr>
<td>DIT</td>
<td>Di-iodo tyrosine</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>FT3</td>
<td>Free tri-iodothyronine</td>
</tr>
<tr>
<td>FT4</td>
<td>Free thyroxine</td>
</tr>
<tr>
<td>FT4I</td>
<td>Free thyroxine index</td>
</tr>
<tr>
<td>FT31</td>
<td>Free triiodothyronine index</td>
</tr>
<tr>
<td>HCG</td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
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<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>MIT</td>
<td>Mono idotyroline</td>
</tr>
<tr>
<td>MRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>NTIs</td>
<td>Non thyroidal illness syndrome</td>
</tr>
<tr>
<td>RAIU</td>
<td>Radio iodine uptake</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
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</tr>
<tr>
<td>RIA</td>
<td>Radio immunoassay</td>
</tr>
<tr>
<td>RT3</td>
<td>Reverse tri-iodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>T3</td>
<td>Tri-iodothyronine</td>
</tr>
<tr>
<td>TT4</td>
<td>Total Thyroxine</td>
</tr>
<tr>
<td>TT3</td>
<td>Total triiodothyronine</td>
</tr>
<tr>
<td>TBG</td>
<td>Thyroxine binding globulin</td>
</tr>
<tr>
<td>TBPA</td>
<td>Thyroxine binding prealbumine</td>
</tr>
<tr>
<td>THBR</td>
<td>Thyroid hormone binding ratio</td>
</tr>
<tr>
<td>TTR</td>
<td>Trans-thyretin</td>
</tr>
<tr>
<td>TR</td>
<td>Thyroid receptor</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin releasing hormone</td>
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<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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</table>
This is prospective, case control, hospital based study was conducted at Khartoum Teaching Hospital and El Shaab Teaching Hospital in the period October 2004 to January 2005.

In this study, serum thyroid hormone levels (TSH, TT4, TT3, FFT4 and FT3) were measured using a sensitive chemiluminescence immunoassay automated system and kits (immulite®) in 60 hospitalized patients suffering from acute or chronic systemic non-thyroidal illness and 21 apparently healthy individuals as controls. Selection criteria were satisfied by hospitalized patients who had no past history or family history of thyroid disease nor evidence of clinical and/or laboratory abnormalities suggestive of primary thyroid or pituitary dysfunction.

The objective of this study was to determine the pattern of alteration in thyroid hormone economy in various non-thyroidal illnesses in Khartoum Sudan and also to correlate these alterations with the severity of illness and therapeutic drugs used.

The results were compared with both reference ranges provided by the Immulite ® manufacturer with its kits and results obtained on control subjects. The study concluded that there was a statistically significant reduction in total triiodothyronine levels and free triiodothyronine levels in 38 (63.33%) and 32 (52.33%) respectively and elevated thyroxine levels in 12 (20%) of patients.
In spite of these alterations TSH levels were normal in 55 (91.67%) of studied patients.

The study also categorized patients into groups: Those who had low T3 only; those had elevated T4 only; a group who had low T3 and T4 and a group who had low T3,T4 and TSH. It was also found that the degree of alteration of thyroid hormone levels appears to be correlated with the severity of the disease and the administration of some drug which affect thyroid hormone economy.

Finally this study recommends that large prospective, carefully controlled studies should be done to monitor thyroid function test findings during and after recovery from NTI.

The study also recommends that thyroid function tests should not be requested during illness unless there is strong evidence of coexistence of thyroid disease, and should be repeated when non-thyroidal illness is resolved and that the request form should contain all relevant clinical information, and that close contact between clinicians and pathologists be maintained to facilitate good interpretation of test results and also that every lab should establish its own reference range.
الشعبة ومستشفى التعليمي الخtram في أجرية تحليلية مقارنة دراسة هذه أكتوبر بين ما الفترة في التعليمي 2004 يناء إلى 2005 م.

اختيار تم دراسة هذه في 60 ميت يعانون الذين في المرضى من حالة مزمنة أو حدث أمراض.

اختيار وآثاما 21 افراد من حالتهم (لقياس الدقيرة الغدة الهرمونات (TSH, TT4, TT3, FT3, FT4) يُعزى تحديداً كبا ن. (Controls)

يُذكر أن KIDNJA� أذ أدي للمريض في أوقات الدراسة في السودان في الأخرة العضوية للمريض - على أن أسباع فأربعين يومًا.

1. لس العيادة العيادة أعيد النظر في النتائج تمت ثالث T3  أ (FT3) نتائجه في ذ ٪63.33  ٪32  ذ ٪63.33  ذ ٪38  في ذ (OS)

2. أذ أدي للتيات TT4 أذ لجرّاب النتائج لحالة .٪20  ذ ٪512 (2 ليت بور. في ذ ٪91.67) ذ ٪55 في أضواء. عشرة ، أن TSH TSH T3) أدنى يزيد T3، T4 (أدنى أن تزيد T3، T4، TSH) أدنى (أدي وأدنى T4).
عانى الأثر على تلك العقاقير واستخدام المريض حدث بين العلاقة كذلك أنه خلصت أيضاً الأهرمونات هذه متسوية في حديثة التغييرات ومؤقتة القدرة التشغيل.

بدأت النوبة في تحدث هذه المن أكبر بصور أخرى دراسة بإجراء مدة شفاء وبعد أوصت وآيضًا أصابت وجاءت في库里 كذلك كأن إذا المريض أثناء الغدة وظيفة لمراقبة تحكم ظروف.

بعد أن أوصت وأيضًا الإصابة وجاءت في هذه المن وأكبر بصور أخرى دراسة في الرصف أنه يعم النوبة أثناء الأهرمونات فإنه في.

بيرة إذا المريض، شفاء عند الفحص ذلك تم وإذا الدقية الغدة في.

لم تكن بألواح نفسية أن هناك فحص لحظة بعد ذلك ودعوته الجدة بين العلاقة كذلك الأثار المريضة، شفاء عند الدقيقة المعلم ومعنوي.
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1.1. Anatomic and functional embryology:

The human thyroid gland is first recognizable about one month after conception when the embryo is approximately 3.5 to 4 mm in length.

The embryogenesis and certain aspects of the thyroid function are closely interlinked with the gastrointestinal tract\(^1\).

Thyroid tissue is present in all vertebrates. In mammals the thyroid originates from an evagination of the floor of the pharynx, and a thyroglossal duct marking the path of the thyroid from the tongue to the neck sometimes persists in the adult\(^2\).

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults\(^3\). The normal thyroid is made up of two lobes joined by a thin band of tissue, the isthmus. Two connective-tissue capsules enclose the gland. The outer is not well defined and attaches the thyroid to the trachea. On the posterior surface of the thyroid, the two pairs of parathyroids are situated between the two capsules\(^4\). Two pairs of vessels constitute the major arterial blood supply, namely the superior thyroid artery, arising from the external carotid artery, and
the inferior thyroid artery, arising from subclavian artery. Estimates of thyroid blood flow range from 4 to 6 ml/min/gm.\(^{(1)}\)

The thyroid is innervated by both adrenergic and cholinergic nervous systems via fibers arising from the cervical ganglia and vagus nerve, respectively.\(^{(1)}\)

1.2. Histology:

The functional unit of the gland is the thyroid follicle or acinus. This consists of cuboidal epithelial cells arranged as roughly spheroidal sacs, the lumen of which contains colloid.\(^{(4)}\)

The height of follicular cells varies among follicles depending on their state of activity. In highly active follicles, the epithelium is mainly cuboidal, whereas in less active follicles the epithelium appears flattened.\(^{(5)}\) Each follicle is surrounded by a basement membrane and the parafollicular, calcitonin-secreting, c-cells lie between this membrane and the follicular cells.\(^{(4)}\) The c-cells produce the polypeptide calcitonin, which is involved in calcium regulation. From 20 to 40 follicles are demarcated by connective tissue septa to form a lobule supplied by a single artery. The function of a lobule may vary from that of its neighbors.\(^{(1)}\) Microvilli project into the colloid from the apexes of the thyroid cells, and canaliculi extend into them. There is a prominent
endoplasmic reticulum, a feature common to most glandular cells and secretory droplets of thyroglobulin are seen.(1, 4)

1.3. Formation and secretion of thyroid hormones:

The principal hormones secreted by thyroid are thyroxine (T4) and tri-iodothyronine (T3). (2, 3) T3 is also formed in peripheral tissues by deiodination of T4; both hormones are iodine-containing amino acids. A small amount of reverse tri-iodothyronine (3, 3', 5'-tri-iodothyronine, RT3) is also found in thyroid venous blood. T3 is more active than T4, whereas RT3 is inactive(2) about 93 percent of metabolically active hormone secreted by the thyroid gland is thyroxine, and 7% tri-iodothyronine. Tri-iodothyronine (T3) is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for much shorter time than does thyroxine. (3)

Iodine is the most important element in the biosynthesis of thyroid hormones. Approximately 150 mg of iodine is absorbed in the intestine each day. The thyroid gland has a very high attraction for iodine and traps about 70 mg/day at the base of the cell by active transport. The iodide is then transported to the follicular lumen. The iodide molecule is oxidized by peroxidase, presumably at the interface of the cell and the lumen, to a more reactive form, I° or I\. This form combines with the glycoprotein thyroglobulin. (6) This glycoprotein is made up of two subunits and has a molecular weight of 660,000. It contains 10% carbohydrate by weight, and also contains 123 tyrosine residues, but only four to eight of these are normally incorporated into thyroid hormones. (2)

Thyroglobulin acts as a preformed matrix containing tyrosyl groups to which the reactive iodine attaches to form the hydroxyl residues of monoiiodotyrosine (MIT) and diidiotyrosine (DIT).

The next step is the enzymatic coupling of the iodinated tyrosine molecules, catalyzed by peroxidase to form T4 or T3. The coupling of two DIT molecules forms T4. The coupling of one DIT molecule and one MIT molecule result in the formation of T3 (3, 5, 3'-T3) or reverse T3 (rT3) of (3, 3', 5'-T3). (6)

1.4. Storage and release of hormones:

After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules, in this form, the thyroid
hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 - 3 months. Release of thyroid hormones involves pinocytosis of the colloid by follicular cells, fusion with lysosomes to form phagocytic vacuoles and proteolysis.\(^7\) Thyroid hormones are hence released into blood stream. Proteolysis also results in the liberation of mono and di-iodothyronines (MIT and DIT), these are usually degraded within thyroid follicular cells and their iodine is retained and re-utilized. A small amount of thyroglobulin also reaches the blood stream.\(^7\)

Thyroid hormones in the blood are transported almost completely bound to specific binding proteins. The bound forms of the hormones are inactive.\(^7,8\) The bound form of T4 accounts for 99.97\% of all T4, and the bound form of T3 accounts for 99.8\% of the circulating level of the hormone, only 0.03\% of T4 and 0.2\% of T3 circulate in a free non-protein bound, form.\(^8\) T4 and T3 are bound in a firm but reversible bond to several proteins, all of which are synthesized in the liver.\(^9,10\) There are three thyroid hormone binding proteins, thyroxine binding globulin (TBG), transthyretin in (TTR) thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA).\(^7,8\) T4 binds predominately to TBG, (70\% - 75\%), to a lesser extent to TTR (15\% - 20\% and to a slight extent to
albumin (10%). T3 is bound by TBG and TBA but very little by TTR. Normally, only one third of the available protein binding sites are occupied by the thyroid hormones.\(^7\)

The amounts of thyroid-binding proteins vary in some physiologic and pathologic state,\(^8\) e.g. TBG is increased during pregnancy, genetically or by estrogen. It may decrease due to genetic absence, protein losing states causing disease, severe illness, acromegaly and androgens.\(^6\)

The binding globulins serve to increase the duration of the hormones in plasma by protecting them from degradation and renal excretion. They also buffer the organism from abrupt changes in hormone level.\(^8\) The binding may also reduce the amount of thyroid hormones lost through the kidneys and it has been suggested that the binding protein may have a specific role in facilitating hormone uptake by cells.\(^7\)

**1.5. Metabolism of thyroid hormones:**

The most important pathway for metabolism of T4 is the monodeiodination of its outer ring to form the active thyroid hormone T3.\(^{11, 12}\) Inner-ring deiodination of T4 and T3 and further deiodination reactions deactivate the hormones.\(^{13, 14}\)

One-third of the circulating T4 is normally converted to T3 in adult humans, and 45% is converted to RT3, only about 13% of
circulating T3 is secreted by the thyroid and 87% is formed by deiodination of T4. Similarly, only 5% of circulating RT3 is secreted by the thyroid and 95% is formed by deiodination of T4. Two different enzymes are involved, 5- deiodinase catalyzing the formation of T3 and 5- deiodinase catalyzing the formation of RT3. Three deiodinases have been identified in mammalian tissues.

Deiodinases 1 and 2 (D1 and D2) catalyze outer-ring monodeiodination, thereby producing T3. D1 also catalyzes removal of an inner-ring iodine from T3 and T4 prefers and the sulfated derivatives as substrates. The type 3 deiodinase (D3) is an obligate inner ring monodeiodinase with a preference for T3 as substrate. The deiodinase in liver and kidney microsomes is a type I iodothyronine deiodinase (5-D1).

Type II deiodinase (5- D II) is found in the brain, the pituitary and brown fat. Type III deiodinase (5-DI) is found in the placenta and brain. 5' - DI is unique in that it contains the rare amino acid slenocystine in which the sulfur in cysteine is replaced by selenium i.e. it is a selonoprotein. In the liver, T4 and T3 are conjugated to form sulfate and glucuronides. These conjugates enter the bile and pass into the intestine. The thyroid conjugates are hydrolyzed, and some are reabsorbed, but some are excreted
in the stool. In addition, some T4 and T3 pass directly from the circulation to intestinal lumen.\(^{(2)}\)

1.6. Regulation of thyroid hormones:

The hypothalamic-pituitary-thyroid axis (HPTA) is the neuroendocrine system that regulates the production and secretion of thyroid hormones.\(^{(6)}\) In addition, there is an inverse relationship between the glandular organic iodine level and the rate of hormone formation. Such autoregulatory mechanisms serve to stabilize the rate of hormone synthesis despite fluctuations in the availability of substrate such as iodine.\(^{(1)}\)

Regulation of the thyroid begins with the hypothalamus. Thyrotropin-releasing hormone (TRH) is a tripeptide released by the hypothalamus. It travels along the hypothalamic stalk to the beta cells of the anterior pituitary, where it stimulates synthesis and release of thyrotropin or thyroid stimulating hormone (TSH).\(^{(6)}\) TRH binds to a receptor in thyrotrope membrane\(^{(17,18)}\) for induction of the thyrotrope response.\(^{(1)}\) The neuron bodies producing TRH are innervated by catecholamine, neuropeptide and somatostatin-containing axons, all of which potentially influence the rate of synthesis of the prepro-TRH molecule.\(^{(1)}\) T3 suppresses the level of
prepro-TRH mRNA by T3 in the hypothalamus,\(^{(19,20)}\) but normal feedback regulation of prepro-TRH mRNA synthesis by thyroid hormone required a combination of T3 and T4 in the circulation, the latter giving rise of T3 via direct local synthesis in the central nervous system at the pituitary level.\(^{(20)}\) The secretion of TSH seems to be regulated by an interplay of negative feedback from circulating free T3 and T4, TRH, and inhibitory hypothalamus neurotransmitters, such as somatostatin and dopamine.\(^{(21,22)}\)

TSH is a glycoprotein secreted by the thyrotropes in the anteromedial portion of adenohypophysis. TSH is composed of an alpha-subunit of about 14 kd that is common to luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotrophin (HcG) and a specific beta-subunit that in the case of TSH, is a 112 amino acid protein.\(^{(23,24)}\) TSH acts like other polypeptide hormones in that when it binds with receptor sites, it activates adenyl cyclase, which then catalyses a reaction to produce cyclic adnosine monophosphate (AMP).\(^{(25,26)}\) The biologic half-life of human TSH is about 60 minutes. TSH is degraded mostly in the kidney and to a lesser extent in the liver.\(^{(1,2)}\)

TSH is the main stimulus for the uptake of iodide by the thyroid gland and also stimulates the activation of the protease enzymes, which in turn catalyze the hydrolysis of thyroglobulin, the
storage forms of T4 and T3. TSH also acts to increase the size and number of follicular cells.\(^7\)

Trh acts in the thyrotrope to stimulate the release and later synthesis of TSH, while thyroid hormones (T3, T4) inhibit these functions.\(^1\)

The influence of iodine availability, in contrast to the feedback control effected via TSH which maintains the plasma or tissue concentration of the thyroid hormones, acts as an intrinsic autoregulatory mechanism to maintain the constancy of thyroid hormone stores and also plays a role in the capacity of the thyroid to overcome factors that impair hormone synthesis.\(^1\)

1.7. Mechanism of action:

Thyroid hormones enter cells, and T3 binds to thyroid receptors (TR) in the nuclei. T4 can also bind but not as avidly. The hormone-receptor complex then binds to DNA via zinc fingers and affects the expression of a variety of different genes that code for enzymes, which regulate cell function. Thus, the nuclear receptors for thyroid hormone are members of the superfamily of hormone-sensitive nuclear transcription factors.\(^2\)

1.8. Effect of thyroid hormones:

Thyroid hormone actions include calorigenesis and oxygen consumption by means of regulation of carbohydrate, lipid and
protein metabolism. They also control nervous system activity and brain development, cardiovascular stimulation, bone and tissue growth and development, gastrointestinal regulation and sexual maturation.\(^{(2,3,6)}\) So the thyroid gland is essential for normal growth and development and has many effects on metabolic processes.\(^{(7)}\)

1.9. Clinical considerations:

These embrace metabolic manifestations of thyroid disease related either to excessive or inadequate production of thyroid hormones. The clinical syndrome that results from hyperthyroidism is thyrotoxicosis. The term myxodema is often used to describe the entire clinical syndrome of hypothyroidism, but it strictly refers to the dryness of the skin.\(^{(7)}\)

1.9.1. Thyrotoxicosis:

The term thyrotoxicosis refers to the biochemical and physiological manifestations of excessive quantities of the thyroid hormone.\(^{(1)}\) The term hyperthyroidism is reserved for disorders that result from over production of hormone by the thyroid itself, Grave's disease being the most common. The manifestations depend on the severity of the disease, the age of the patients, the presence or absence of extrathyroidal manifestations and the specific disorder producing thyrotoxicosis.\(^{(1)}\)
The symptoms found in thyrotoxicosis are related to the catabolic-hypermetabolic effects of thyroid hormones or the increased metabolic activity in various tissues and increased sensitivity to catecholamines.\(^{(27)}\)

The symptoms may include nervousness, irritability, insomnia, fine tremor, excessive sweating, heat intolerance, flushed face, pruritus, tachycardia, frequent bowel movements, hyperkinesis, weight loss that occurs even though the patient eats well, gynecomastia, oligomenorrhoea; amenorrhea; decreased libido, loss of muscles mass, loss of fat stores producing an increase in plasma fatty acids, a decrease in serum cholesterol and LDL lipoprotein\(^{(9)}\) and apolipoprotein B,\(^{(28)}\) a tendency toward ketosis, a negative nitrogen balance, exercise intolerance, easy fatigability, dyspnoea on exertion and a warm and moist skin with patchy depigmentation.\(^{(7)}\) There may also be a recession of the nails from the nail beds, clubbing of the fingers and toes and swelling of the subcutaneous tissues.\(^{(29,30)}\) The hematological manifestations include a decrease of the white blood cells count because of a decrease of neutrophils. Lymphocytosis also occurs. The patient may be physiologically ‘anaemic’ despite an increased red blood cell mass due to excess demand for oxygen.\(^{(26)}\) Approximately 20% of the patients have hypercalcemia an
subsequent polyuria. Long term risks include abnormal bone metabolism leading to osteoporosis, and the development of cardiac atrial fibrillation, and exophthalmus.\textsuperscript{(3,6)}

Causes of thyrotoxicosis can be divided into two subcategories based on results of the radioactive iodine uptake (RAIU) test. Uptake is increased (or normal) in Grave's disease, toxic multinodular goiter, TSH secreting tumors, trophoblastic tumours and toxic adenoma. RAIU is suppressed in subacute thyroiditis, silent thyroiditis, chronic thyroiditis, struma ovarii, metastatic thyroid carcinoma or as a result of excessive circulating iodine (e.g. from x-ray dyes, medications or absorption through the skin.\textsuperscript{(31, 32)}

1.9.2. Hypothyroidism:

Hypothyroidism occurs when there are insufficient levels of thyroid hormones to provide metabolic needs at the cellular level.\textsuperscript{(6)} The incidence of hypothyroidism in the United State is about 0.5\%,\textsuperscript{(33,34)} and it affects females about four times as often as males. Congenital hypothyroidism exists at a rate of around 1 in 4000 births.\textsuperscript{(35,36)}

Many structural or functional abnormalities can impair production of thyroid hormones and cause the clinical state termed hypothyroidism. The causes can be divided into three main
categories: (1) Permanent loss or atrophy of thyroid tissue (primary hypothyroidism) (2) hypothyroidism with compensatory thyroid enlargement due to transient or progressive impairment of hormone biosynthesis (goitrous hypothyroidism), and (3) insufficient stimulation of normal gland as a result of hypothalamic or pituitary disease or defects in the TSH molecule itself (control or central hypothyroidism). Primary and goitrous hypothyroidism account for approximately 95% of cases; only 5% or less being due to TSH deficiency.\(^{(1)}\)

Hypothyroidism can be manifested in all organ systems, and these manifestation are largely independent of the underlying disorder, but are functions of the degree of hormone deficiency.\(^{(1)}\) Symptoms of hypothyroidism include enlargement of the thyroid gland or goiter, impairment of cognition (including memory, speech and attention span), fatigue, slowing of mental and physical performance, changes in personality, intolerance to cold, exertional dyspnoea; hoarseness, constipation, decreased sweating, easy bruising, muscle cramps, paresthesias, and dry skin. Hypothyroidism has been shown to be associated with increased cholesterol, LDL lipoprotein (a), apolipoprotein (b), and an increased risk of coronary heart disease. As the disease progresses into severe hypothyroidism, these features worsen and
the condition is referred to as myxodema, which describes non-pitting swelling of the skin.\textsuperscript{(6)}

1.10. **Tests of thyroid function:**

Laboratory evaluation can be divided into five major categories: (1) direct tests of thyroid function that provide information about the handling of iodine. (2) Tests that assess the state of the hypothalamic pituitary thyroid axis. (3) Tests that assess the concentration and binding of the thyroid hormones in the blood, (4) tests that assess the impact of thyroid hormones on tissues and (5) Miscellaneous tests.\textsuperscript{(1)}

1.11. **Exogenous and endogenous factors that influence thyroid hormone economy:**

1.11.1. **Pregnancy and maternal-fetal interaction:**

Pregnancy affects virtually all aspects of thyroid hormone economy.\textsuperscript{(37,38,39)} The total serum T4 and T3 concentration rise to levels twice those of non-pregnant women, owing to the increase in TBG concentration in the first trimester.\textsuperscript{(40,41)}

Free-T4 and T3 levels also increase slightly during the first trimester, but return to normal by about 20 weeks of gestation and remain so until delivery.\textsuperscript{(37,39,42)} This pattern coincides with that of hCG levels in the first trimester.\textsuperscript{(43,44)} A slight decrease in serum TSH during the first trimester indicates that the free T4 and T3
changes are not dependant on the hypothalamic pituitary axis.\textsuperscript{(45,46,47,48)} Owing to the increase in the glomerular filtration rate (GFR) iodide clearance increases during gestation, leading to increased dietary requirements. If these requirements are not met T4 falls, TSH increases and goiter ensues. There is no clinically significant change in the size of the thyroid during pregnancy in normal women receiving adequate quantities of iodide.

1.11.2. Age:

Thyroid hormone production rates are higher per unit of body weight in neonatal infants and children than in adults. When expressed on a body/weight basis the daily levothyroxine requirement is about 10mg/kg in the newborn, decreasing to about 1.6 mg/kg in adult. Requirements remain stable, except for an increase during pregnancy, until the seventh to eight decades when the T4 production rates decrease to 20%.\textsuperscript{(49,50)}

1.11.3. Glucocorticoids:

Both corticotrophin (adrenocorticotropic hormone "ACTH"), through its action on the adrenal cortex, and glucocorticoids influence thyroid function. Pharmacologic doses of these agents decrease the thyroid RAIU, iodide clearance, and turnover rate. The fact that these alterations can be reversed by the
administration of exogenous TSH suggests, that glucocorticoids suppress pituitary TSH secretion.\textsuperscript{(1)}

1.11.4. Gender and gonadal steroids:

Thyroid diseases are more common in women than in men, and goiter commonly develops during puberty, during pregnancy and after the menopause.\textsuperscript{(51,52)} Responses of TSH to TRH are greater in women than in men especially in women older than age 40 years. Estrogen appears to enhance the response to TRH, possibly by increasing the number of TRH receptors in the thyrotropic cells, but responses to TRH do not vary materially during the menstrual cycle.\textsuperscript{(53,54)}

1.11.5. Growth hormone:

Growth hormone does cause an increase in serum free T3 and a decrease in free T4 in both T4 treated and normal individuals, suggesting increased conversion of T4 to T3.\textsuperscript{(55)}

1.11.6. Environmental factors:

Repeated exposure to extreme cold for several months causes a decrease in the total serum T4 concentration, but no change in free T4. Total but not free T3 also decreases, suggesting that this could be explained by a decrease in TBG. Only small seasonal variations in serum T4 and T3 concentration occur in normal subject.\textsuperscript{(56)}
1.11.7. Nutrition:

Both short term and long term alteration in nutritional state affect various aspects of thyroid hormone economy especially peripheral hormone metabolism. When euthyroid lean or obese subjects are starved the serum total and free T3 can decrease to subnormal levels.\(^{(57, 58)}\) By contrast, total T4 concentration remains essentially unchanged or increases slightly because of a modest decrease in iodothyronine binding. As serum T3 concentration decreases, the concentration of rT3 increases reciprocally usually to values about twice normal (due to decreased clearance). Despite the decrease in free T3 concentration with starvation, the basal serum TSH concentration and the response to TRH are essentially unaffected.\(^{(59, 60, 61)}\) It seems most likely that TRH secretion is reduced by starvation and that this is the best explanation for these phenomena. Chronic malnutrition, as in protein calorie malnutrition and anorexia nervosa is also associated with a decrease in serum T3 concentration, serum T4 level also tends to be slightly decreased, but serum TSH concentrations and their response to exogenous TRH are usually normal. In contrast, over-feeding, particularly with carbohydrate, increases the T3 production rate, increases the serum T3 level, lowers the serum rT3 concentration and increases basal thermogenesis.\(^{(62)}\)
1.12. Effects of illness (Euthyroid sick syndrome):

Euthyroid sick syndrome can be described as abnormal findings on thyroid function tests in the setting of non thyroidal illness (NTI) without preexisting hypothalamic pituitary and thyroid dysfunction and after recovery from an NTI, these thyroid function test result abnormalities should be completely reversible.\(^{63}\)

Abnormal thyroid hormone levels have been described in the presence of heart failure, chronic renal failure, liver disease, stress, starvation, surgery, trauma, infections and autoimmune diseases as well as with use of a number of drugs,\(^{64}\) in gastrointestinal disease, pulmonary diseases, malignancy and bone marrow transplantation. Multiple alterations in serum thyroid function test findings in patients with a wide variety of NTI without evidence of preexisting thyroid or hypothalamic pituitary disease have been described. The most prominent alterations are low serum (T3) and elevated (rT3), leading to the general term low T3 syndrome. Thyroid stimulating hormone (TSH), thyroxine (T4), free T4, and free T4 index (FTI), are also affected to variable degrees based on the severity and duration of the NTI, as the severity of NTI increases, both serum T3 and T4 levels drop and gradually normalized as the patient recovers.
Figure shows changes in thyroid tests during the course of non-thyroidal illness

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NACB: Laboratory Support for the Diagnosis and Monitoring of thyroid Disease

1.12.1. Types of abnormalities:
1- **Low T3:** this is most commonly encountered abnormality in non-thyroidal illness. T3 levels fall rapidly within 30 minutes to 24 hours of onset of illness, while rT3 level increases.(64,65) Thyrotropin (TSH) and total and free T4 level are usually normal. Low T3 syndrome is thought to be due to a decrease in T4 conversion to T3 by the hepatic deiodinase system, thus inhibiting the generation of T3 and preventing the metabolism of rT3. (66) The finding of increased rT3 levels differentiates this syndrome from true hypothyroidism, in which rT3, T3 and T4 levels would most likely all be low, an exception is in patients with advanced AIDS, in whom baseline rT3 level are already low.(64)

2- **Low T3 and low T4:** in patients who are moderately ill, low T3 levels are accompanied by low T4 levels. This has been described in up to 20% of patients treated in intensive care units.(63) Free thyroid hormone level are usually normal but may be decreased in patients treated with dopamine hydrochloride or corticosteroids. TSH levels may also be normal to low. The mechanisms involved may be a deficiency in TBG, which leads to low total thyroid hormone levels. Another possibility is the presence of a thyroid hormone binding inhibitors, which lower total thyroid hormone levels. A marked decrease in serum T4 is
associated with a high probability of death, when serum T4 levels drop below 4 mg/dl the probability of death is about 50%; with serum T4 levels below 2 mg/dl, the probability of death reaches 80%.\(^{(67,68)}\)

3- **Low TSH, low T3, and low T4:** this abnormality occurs in patients with the most severe non-thyroidal illness. Although most of these patients have TSH levels at the lower end of normal, TSH may be undetectable in some. The findings of low TSH and low total T4 and T3 levels suggests altered pituitary or hypothalamic responsiveness to circulating thyroid hormone levels. During the recovery period TSH levels return to normal or may even rise transiently before returning to normal.\(^{(69,70,71)}\)

4- **Elevated T4:** in this condition the total T4 level is elevated, TSH level is normal or elevated and T3 is normal or high. It may be seen in primary biliary cirrhosis and acute and chronic active hepatitis in which TBG synthesis and release are increased.\(^{(72)}\) Elevated levels of total and free T4 have been reported in patients with acute psychiatric illness.\(^{(73)}\) Drugs such as amiodorone hydrochloride (cardarone), propranolol hydrochloride (inderal), and iodinated contrast agents also elevate T4 levels by inhibiting peripheral conversion of T4 to T3.
5- Free T3 and free T4: most studies have found free T3 hormone to be depressed and free T4 within the reference range low or high.\(^{(63)}\)

1.12.2. Pathophysiology:

*Proposed mechanisms explaining abnormalities in thyroid hormone levels:*

1. **Accuracy of test assays in nonthyroidal illness:**

   Abnormalities of thyroid function test results might represent test artifacts or true abnormalities. According to one proposition, the assays would indicate reference range thyroid hormone levels in the blood if appropriate tests were applied.\(^{(63)}\)

2. **Inhibition of thyroid hormone binding to thyroid-binding proteins and tissues:**

   Some authors propose that serum thyroid hormone abnormalities are due to inhibition of thyroid hormone binding to proteins, thus preventing tests from appropriately reflecting free hormone levels. This binding inhibitor can be present both in the serum and in body tissues and might inhibit uptake of thyroid hormones by cells or prevent binding to nuclear T3 receptors, thus inhibiting the action of the hormone. This inhibitor is associated with the non-esterified fatty acid fraction in the serum.
Contrary to this proposition, substantial evidence indicates that, in an in vivo state, the levels of binding inhibitors do not reach levels sufficient to influence the circulating levels of free T4, even in patients who are severely ill. Also, some studies have failed to demonstrate an existing binding inhibitor. (65)

3- Cytokines:

Cytokines are thought to play a role in NTI-particularly interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, and interferon-beta. Cytokines are though to affect the hypothalamus, the pituitary, or other tissues, inhibiting production of TSH, thyroid-releasing hormone (TRH), thyroglobulin, T3, and thyroid-binding globulins. Cytokines are also thought to decrease the activity of type I deiodinase and to decrease the binding capacity of T3 nuclear receptors. (74, 75, 76, 77)

4- Deiodination:

Peripheral deiodination of T4 to T3 is impaired, largely secondary to decreased activity of type I deiodinase enzyme, which deiodinates T4 to T3. Diminished enzyme activity accounts for decreased deiodination of T4 to T3. (78)

An alternative explanation is that reduced tissue uptake of T4 secondary to deficiency of cytosolic cofactors (e.g. nicotinamide adenine dinucleotide phosphate, glutathione) results in decreased
substrate for type I deiodinase enzyme. Type I deiodinase is a selenium protein; because selenium deficiency is common in critically ill patients, some propose that selenium deficiency may contribute to type I deiodinase malfunction.\(^{(79)}\) Cytokines (e.g. IL-1 beta, TNF-alpha, interferon-gamma) decrease type I deiodinase messenger RNA in vitro. Type I deiodinase does not exist in the pituitary where T3 levels are within the reference range, because of enhanced local deiodination. This indicates that an enhancement of intrapituitary T4 to T3 conversion exists due to pituitary-specific and brain-specific type II deiodinase.

5- Inhibition of thyroid-releasing hormone and thyroid-stimulating hormone secretion:

Cytokines, cortisol, and leptin, as well as changes in brain thyroid hormone metabolism, affect inhibition and secretion of TRH and TSH. Considerable evidence suggests that an alteration in hypothalamic and pituitary function cause low production of thyroid hormone. In rats, starvation reduces hypothalamic messenger ribonucleic acid (mRNA for TRH, reduces portal serum TRH, and lowers pituitary TSH content.\(^{(80)}\) A recent study also documents low TRH mRNA in hypothalamic para-ventricular nuclei in NTI patients.\(^{(81)}\)

6- Inhibition of plasma membrane transport of iodothyronines:
Serum factors, such as bilirubin, nonestrified fatty acids (NEFA), furanoic acid, hippuric acid, and indoxyl sulphate, which are present in various NTIs, have been shown to inhibit transport of thyroid hormones.

7- Thyroxine-binding globulin decreases and desialation:

T4 binding globulin (TBG) is a member of the serine protease inhibitors. Diminished T4 in NTI has been proposed to be due to low TBG caused by protease cleavage at inflammatory sites in acute inflammatory conditions. One other hypothesis for the cause of disproportionately low serum T4 concentrations in patients with NTI is the presence of abnormal serum binding due to desialation of TBG.(63)

8- Other factors altering serum T4 supply:

Administration of glucagon caused a significant fall in serum T3, suggesting that the stress-induced hyperglucagonemia may be a contributor to the NTIS syndrome by altering intracellular metabolism of T4.(82)

Dopamine given in support of renal function and cardiac function must play a role in many patients who develop low hormone levels, while in an intensive care unit setting. Dopamine inhibits TSH secretion directly, depresses further the already abnormal thyroid hormone levels, withdrawal of dopamine infusion...
is followed by prompt dramatic elevation of TSH, a rise in T4 and T3 and increase in the T3/rTs ratio.\textsuperscript{(65)}

9- **Drugs that influence thyroid function:**

Drugs that decrease TSH secretion: e.g. dopamine, glucocorticoids and octreotide.

Drugs that decrease thyroid hormone secretion: lithium, iodide, and aminoglutethimide.

Drugs that increase thyroid hormone secretion: iodide and amiodarone.

Drugs that decrease thyroxine absorption: colestipol, cholestyramine, aluminum hydroxide, ferrous sulphate and sucralfate.

Drugs that alter thyroxine and triiodothyronine transport in serum: estrogens, tamoxifen, heroin, methadone, mitotine and fluorouracil.

Drugs that alter thyroxine and triiodothyronine transport in serum (decreased serum thyroxine-binding globulin concentration): androgens, anabolic steroids, slow-release nicotinic acid and glucocorticoids.

Drugs that alter thyroxine and triiodothyronine transport in serum (displacement from protein-binding sites): furosemide, fenclofenac, mefenamic acid and salicylates.)
Drugs that alter thyroxine and triiodothyronine metabolism (increased hepatic metabolism): phenobarbital, rifampin, phenytoin and carbamazepine.

Drugs that decreased thyroxine and triiodothyronine metabolism by decreased thyroxine 5-deiodinase activity e.g. amiodarone, proylthiouracil and beta adrenergic antagonist.

Certain thyroid function test result abnormalities also have been characterized in the conditions and NTIs discussed as follows:

1- **Thermal injury**: patients with significant burns exhibit typical euthyroid sick profile values, i.e. low T3 and FT3 with increase rT3; total T4 and free T4 levels may be slightly decreased acutely, but normalize after a few days. Basal TSH secretion is unchanged. \(^{(63)}\)

2- **Surgery**: total T3 falls dramatically on the day of surgery and remains significantly decreased postoperatively. The degree of the fall is related to the severity of surgical trauma, an absolute percent increase of free T3, also occurs on the day of the surgery. The free T3 concentration rapidly falls to low levels post operatively, paralleling the decline of total T3. T4 usually is not altered on the day of surgery. One study demonstrated that total T4 decreased during surgery with epidural anesthesia, but
increased with general anesthesia. The percent of free T4 increases during surgery and decrease postoperatively. TSH has been found to be unchanged during surgery except with hypothalamic surgery in which TSH increased.\(^{(63)}\)

3- **Myocardial infarction:** in 1-3 days post infarction, total T3 is low, rT3 is elevated, and basal TSH might be elevated.

4- **Renal disease:** Kaptein, et al \(^{(83)}\) studied patients with acute renal failure and found decreased serum T4 and T3 levels and normal or elevated levels of free T3 and TSH in patients with acute renal failure, but not in those with critical illness. In this group of patients rT3 levels tended to be normal. Ramirez et al \(^{(84)}\) studied patients receiving chronic haemodialysis and found a striking prevalence of goiter (58%) and low serum T4, T3, and TSH levels. In the nephrotic syndrome, clinical presentation and thyroid function test findings mimic hypothyroidism. Total T4 and free T4 levels can be normal or reduced. Total T3 is reduced significantly, free T3 is reduced and rT3 is unchanged in contrast to primary hypothyroidism. Basal TSH either is unchanged or increased slightly, while TSH response to TRH is decreased and delayed.\(^{(63)}\)

6- **Liver disease:** patients with alcoholic liver disease, as reported by Walfish et al \(^{(85)}\) tend to have low serum T3 levels, slightly
reduced T4 levels, and elevated free T4 indexes because of low-binding proteins. In chronic biliary cirrhosis and chronic active hepatitis, as studied by Liewendahl (86) elevated TBG may be found associated with normal free T3 and free T4 levels. Chopra et al (87) studied patients with hepatic cirrhosis and found T4 to be significantly elevated T3 to be markedly reduced, free T3 to be low and TSH to be slightly above normal.

7- **Infection:** in humans, serum T4 and T3 levels fall shortly after the onset of clinical infection. This reflects decreased TSH stimulation of the thyroid, decreased thyroidal secretion, accelerated T4 disappearance and inhibited hormone binding to transport proteins. With recovery, TSH release resumes and T4 and T3 levels progressively rise. (63)

8- **Human immunodeficiency virus infection:** patients with asymptomatic HIV infection or AIDS and without opportunistic infections or hepatic dysfunction have serum T4 and T3 [free T4 concentration also are within the reference range or are slightly low. Some patients may have slightly elevated TBG concentrations, which tend to be inversely related to the percentage of CD4 cells. Some patient may have small increases in serum TSH concentration. Patients with AIDS complicated with Pneumocystis carinii infection or other serious
infections have thyroid function alterations typical of other severe NTI.\(^{63}\)

9- Malignancy: the severity the type and the stage of malignancy affect thyroid function tests in various ways. Effects on thyroid function test results also are associated with nutritional status, medication and treatment type.\(^ {63}\)

1.12.3. Clinical significance:

In patients with the sick euthyroid syndrome, the degree of reduction in thyroid hormone levels appears to be correlated with the severity of non-thyroidal illness and may predict prognosis in some cases.\(^ {64}\) In studies of the low T3 syndrome.\(^ {88}\) The extent and rapidity of the decrease in T3 levels correlated with the mortality rates in patients with tuberculosis. In another study of patients in an intensive care unit, the mortality rate was 84% in those with T4 values less than 3 \(\mu g/dl\) compared with 15% in patients with values above 5 \(\mu g/dl\).\(^ {64}\)

The frequency of thyroid function abnormalities is related to the magnitude of the illness. The most common abnormalities are a T3 reduction, occurring in about 40 -100% of cases of NTI, which parallels the increase of rT3. As the disease severity increases, T4 levels also decrease. Most of patients who are critically ill have reduced T4 levels. In patients who are hospitalized with or without
NTIs about 10% have abnormally low TSH values. The high incidence occurs among the most severely ill group. International frequency is the same as in the United States.\(^{(63)}\)

Mortality and morbidity depend on the underlying NTI, the severity and possibly the duration of the illness. The magnitude of the thyroid function test result abnormalities seem to depend on the severity rather than the type of illness.\(^{(63)}\) T4 is believed to fall in proportion to severity of illness.\(^{(63)}\)

People of all races and both sex are affected equally in NTI. NTI can affect people at any age. The usual aging process appears to influence the responsiveness of various tissues to thyroid hormones, because systemic chronic illnesses are common in individuals of an advanced age, altered metabolism might be responsible for abnormal findings on thyroid function testing in elderly patients experiencing chronic illness.

The examination of each patient with NTI reflects the characteristics of her or his nonthyroidal illness. Thyroid gland examination is unremarkable.\(^{(63)}\)

1.12.4. Lab studies in non-thyroidal illness:

The recommended tests include the following: Total T4, total T3, TSH, Free T3, Free T4, and rT3.

**Total of thyroxine (TT4):**
T4 has routinely been measured by radioimmunoassay (RIA). In the total thyroxine (TT4) RIA methodology, thyroid hormone is first released from the endogenous proteins by the addition of a reagent.

The sample is then incubated with thyroid antibody and labeled ($^{125}$I) T4 in a barbital buffer. After incubation the antigen-antibody bound portion and the remaining free portion are separated, and the labeled bound portion is quantified. Calibrator are run, and the unknowns and controls are extrapolated from standard curve.

Non isotopic immuno-techniques are widely available. The principles of these assays are similar to RIA except that the labeled analyte may be an enzyme as in the enzyme linked immunosorbant assay (ELISA), a flurophore, or chemiluminescence. Other immunotechniques may use a double antibody or a solid-phase system. The enzyme multiplied immunoassay technique is an enzymatic method that does not require separation of the free and bound portions.

Serum TT4 level depends on two other major variables besides rate of thyroid synthesis and release, the first of which is the serum concentration of T4 binding proteins. The other, the peripheral conversion of T4 to T3 and rT3.$^{(6)}$
**Free thyroxine index (FT4 I):**

Calculated free thyroxine index (FT4I) is an indirect measurement of free hormone concentrations and is based on the equilibrium relationship of bound T4 and FT4. The FT4 is calculated by the following formula:

\[ \text{FT4I} = \text{TT4} \times \text{THBR} \]

Which THBR is thyroid hormone binding ratio.

FT4I is an adequate indication of thyroid status and has the advantage of being simple rapid and inexpensive, but the direct free thyroxine assay is better than FT4I in case of extreme protein abnormalities such as congenital TBG excess or deficiency or NTI.\(^6\)

**Measured free thyroxine (FT4):**

Equilibrium dialysis ultra filtration is considered the direct reference method for FT4 determination. It is the most reliable FT4 test in cases in which severe NTI is concurrent with suspected thyroid disease. Although reliable, the method is technically demanding, relatively expensive, and time consuming. It usually used as a confirmatory test.

**Use of FT4 analogs:**
These methods are either one or two step. In the two-step technique, FT4 is immunoeXtracted from serum onto a limited antibody. Next, a washing step eliminated proteins and any other interfering substances. A second labeled hormone is then added, which binds to the unoccupied antibody sites. There is a direct relationship between the patient's FT4 and the amount of bound labeled antibody measured. The one-step immunometric technique is similar to the two-step technique except the labeled analog is chemically modified to prevent it from binding to serum transport protein. FT4 as measured by one-step analog techniques, has been shown to be affected by protein abnormalities such as dysalbuminemia, pregnancy, severe illness, and drugs such as dopamine, amidarone and glucocorticoids.

Fully automated competitive immunoassay is currently available for measurement of FT4. The sample FT4 competes with a chemiluminescent labeled FT4 analog for a limited amount of antibody. Separation occurs through paramagnetic particles in the solid phase that are covalently bound to the antibody. The amount of FT4 in the sample is inversely proportional to the amount of light detected. (6)

**Total T3 and Free T3:**

Total serum T3 is measured by immunometric techniques similar to that of TT4. TT3 is not heavily useful as a primary screening test for hypothyroid disorders because many non-thyroidal factors affecting binding proteins (e.g. NTI) can influence level of TT3. Also depend on the rate of formation from T4 peripheral deiodination, which declines during almost all significant NTIs, stresses, administration of certain drugs and some contrast
media, also FT3 level can be performed along the same manner as FT4 and Free T3 index is calculated similar to FT4.

**Reverse T3:**

Metabolically in active reverse T3 (rT3) also can be measured by immunoassay. Almost all rT3 comes from peripheral deiodination of T4.

RT3 is commonly elevated in patients with NTI in which the TT3 level is often reduced.\(^6\)

**TSH:**

Serum TSH assay is considered to be the first and the best laboratory test for identification of thyroid abnormalities. The monoclonal RIA test was not sensitive enough to distinguish between the very low TSH values found in primary hyperthyroidism from those found in some healthy euthyroid patients. The high sensitivity TSH immunometric assays use two or three separate monoclonal antibodies in the methodologies. The requirement of binding to more then one site gives higher specificity and sensitivity. Each new “generation” of TSH assays is characterized by an approximate ten-fold sensitivity increase compared to the previous one.
Todays second generation for TSH have a sensitivity from 0.1 mu/ml to 0.01 mu/ml. Third generation TSH assays have detection limits of 0.01 mu/ml to 0.005 mu/ml.

A key factor in improvement of sensitivity is incorporation of chemiluminescent labels instead of radioactive isotopes in the assays. Currently, work is under way in the development of a fourth generation of TSH assays.\(^\text{(6)}\)

There are no specific imaging studies that can be used to diagnose NTI.\(^\text{(63)}\) Thyroid sonogram, thyroid uptake and scan and other radiological studies have no role in the diagnosis of NTI.

No typical histological findings of thyroid biopsies in NTI exist. Also no established clinical staging of NTI exists.

The complications depend on the underlying NTI and other organ systems involved.\(^\text{(63)}\)

**1.12.5. Treatment of patients with euthyroid sick syndrome:**

The observed alterations in thyroid studies, which characterized the euthyroid sick syndrome, are generally believed to be adaptive for the individual. Direct support for the probability of their euthyroid status is provided by evidence that these patients do not manifest clinical or laboratory abnormalities suggestive of hypothyroidism.\(^\text{(89)}\) In the euthyroid sick syndrome, the severity of illness has been correlated with the magnitude of changes
observed; the lowest T3 value implying the poorest prognosis for survival.\(^{(90, 91)}\)

The implication here is that the more sick the patient, the more metabolically adaptive may be the low T3 level. Some studies of the adaptive responses of the organisms to acute or chronic illness and the function of the thyroid provide evidence that the response of different tissues to T3 appears to be different in sick than in euthyroid patients due to an altered nuclear T3 binding capacity.\(^{(92,93)}\)

There is evidence that the inflammatory cytokines, present in many disease states, influence the responsiveness of the tissues to thyroid hormones. This is seen at both the nuclear and cytoplasmic level\(^{(94)}\) and could suggest that low T3 and free T3 levels are not the only adaptations in response to illness, but that the responsiveness of the tissues to T3 is also altered. So intervention to correct thyroid hormone levels in patients with serious NTI is controversial, and currently no conclusive studies indicating long-term benefits, in terms of improving morbidity or mortality, from the administration of thyroid hormones to critically ill patients.\(^{(89)}\)

Well-conducted studies performed on fasting patients have provided evidence that the decrease in T3 level is a protective
measure that spares muscle breakdown.\textsuperscript{(95)} Actions of T3 that may improve the metabolic and haemodynamic outcome in the patients with myocardial ischaemia, improve surfactant production in patients with the respiratory distress syndrome, and improve recovery in patients with renal failure are mostly unproven.\textsuperscript{(89)}

A study assessing treatment of such patients with levothyroxine sodium has shown no benefit, which may be due to the inability of these patients to convert administered T4 to the metabolically active T3.\textsuperscript{(96)}

Controlled studies in which liothyronine sodium was administered to patients undergoing coronary bypass procedures showed improvement in cardiac output and lower systemic vascular resistance in one group of 142 patients and no benefit in another group of 211 patients.\textsuperscript{(97,98)}

For all of the reasons discussed above it is believed that there is no indication for the use of thyroid hormone supplementation in critically ill patients whose thyroid hormone abnormalities are consistent with the sick euthyroid syndrome. On the other hand, a judicious trial of therapy with T4 or T3 if the TSH level is elevated to above 5\textmu u/ml, especially if the free T4 concentration is also decreased should be initiated. An argument may be made for using T3 rather than T4 because the sick patients
will only slowly convert the T4 to T3 as a result of the inhibition of 5-deiodinase.\(^{(89)}\)

In patients who are moderately ill intervention, aside from careful monitoring, is not recommended. Thyroid function should be re-evaluated when the thyroid illness is resolved.\(^{(64)}\)

Patients can be assured that this is a transient phenomenon and that normalization of the findings on thyroid function tests are expected with the patient's recovery from NTI.\(^{(63)}\)
JUSTIFICATION

As shown above, results of thyroid function tests are often abnormal in patients who are acutely ill. Interpreting the tests and knowing what to do with the results when there is no other evidence of thyroid dysfunction can be a challenge.

The changes in patients with non-thyroidal illness must be distinguished from those resulting from thyroid disease, a distinction that is essential for appropriate diagnosis and therapy, because some clinicians might consider treatment with thyroid hormone in
hospitalized patients with low serum levels of T4 and T3 which is usually due to euthyroid sick syndrome. Moreover, no similar study was published from Sudan.

OBJECTIVES

To study the pattern of alterations in thyroid hormone economy in various non-thyroidal illnesses in Khartoum, Sudan and also to correlate these alterations with the severity of the illness.
To become familiar with abnormal thyroid function test patterns seen in patients with serious non-thyroidal illness in order to understand appropriate diagnostic tests and treatment approaches for managing thyroid test abnormalities in seriously ill patients.

2. METHODOLOGY
2.1. Study design, area and duration:

This is a prospective case control hospital-based study, conducted at Khartoum Teaching Hospital and El Shaab Teaching Hospital, Khartoum, during the period October 2004 to January 2005.

2.2. Study population:

The study included hospitalized patients with acute or chronic systemic non-thyroidal illnesses and 21 apparently healthy age and sex matched adults as a control group.

2.3 Inclusion criteria:

Hospitalized patients with wide variety of NTI such as liver, cardiovascular, pulmonary and cerebral disease, renal insufficiency, tuberculosis, sepsis, trauma and post surgery.

The patients had no evidence of thyroid disease during their hospital stay.

2.4 Exclusion criteria:

Patients who manifested clinical or laboratory abnormalities suggestive of primary thyroid or pituitary dysfunction.

Patients with a history of thyroid disease, thyroid surgery, radioisotope and known medications used for treatment of thyroid disease such as thyroxine or antithyroid drugs.
Patients with a family history of thyroid disease.

Patients who refused to participate in the study.

2.5 Tools:

2.5.1 Consent:

Verbal consent was taken from the administration of the hospital, treating doctors and from patients or their relative if they were severely ill.

2.5.2 Questionnaire:

A questionnaire (appendix 1) was designed, containing data regarding the personal data, name, age, sex tribe and residence of the patients. It also contains clinical information such as clinical diagnosis, duration of illness, condition of the patient and the drugs used, past medical history and any history of thyroid disease, surgery or medication.

Examination was done to exclude any signs of thyroid abnormalities. The levels of thyroid hormones including total T4 and T3, free T4 and T3 and TSH were then recorded.

2.5.3. Study protocol:

Sixty patients with acute (duration of illness less than two weeks) or chronic (duration of illness more than two weeks) illness. Patients with severe illnesses (multi organ failure, comatose, ICU
patients) and patients with moderate illnesses. 21 apparently healthy adults as controls underwent estimation their serum thyroid hormones levels. The age of study subjects ranged between 18 and 80 years and included both males and females.

2.5.4. Methods of blood collection:

Blood was collected from patients under aseptic conditions. Five ml of venous blood were taken by a disposable syringe and left to clot inside the syringe. Centrifugation was done after complete clot formation had taken place. Serum was separated in a plane container and stored at -20°C until the time of analysis. Grossly Lipaemic or haemolysed samples were excluded.

2.5.5.1. Quantitative measurement of serum thyroid hormones:

This was done by the Immulite® Automated Immunoassay analyzer, which is a continuous flow, random access instrument that performs automated chemiluminescent Immunoassays.

2.5.5.2 Immulite® Product Description and how it works: (appendix 2)

2.5.5.3. Thyroid hormones measurement by the Immulite® analyzer:

1- TSH:

**Principle of the procedure:** Immunometric assay, these assays can be one- cycle or two-cycle. The unlabeled antigen
binds to the immobilized anti-body and is measured after the labeled antibody is added.

**Material supplied:** TSH test unit, each barcode labeled unit contains one bead coated with monoclonal murine anti-TSH and barcoded TSH reagent: 6.5 ml alkaline phosphatase conjugated to polyclonal goat anti-TSH in buffer. Incubation cycle $1 \times 60$ minutes also TSH adjusters which are two vials of lyophilized human TSH in serum/buffer matrix (adjustment interval every four weeks).

Quality control samples used: controls or sample pools with at least two levels (low and high) of TSH.

Expected values euthyroid 0.4 - 4 $\mu$U/ml.

Analytical sensitivity 0.002 $\mu$U/ml.

Linearity: the assay maintains good linearity even at very low concentrations of TSH.

Specificity: the antibody is highly specific for TSH.

2- Total T4:

**Principle of the procedure:** competitive immunoassay, in which the labeled antigen and the unlabeled antigen compete for binding sites on the antibody-coated bead. Under these
conditions, the antibody bound labeled antigen is inversely proportional to the concentration of the unlabeled antigen.

**Incubation cycles:** 2 × 30 minutes.

**Material supplied:** Total T4 test unit. Each barcode labeled unit contains one bead coated with monoclonal murine anti-T4 antibody. Total T4 reagent wedges also with barcoded 6.5 ml alkaline phosphatase conjugated to T4.

Quality control used: controls or sample pools with at least two levels low and high T4 and also by intra-assay and inter-assay precision.

Specificity: The antibody is highly specific for T4.

Linearity the samples were assayed under various dilutions.

‘Normal’ values: 4.5 - 12.5 mg/dl.

Analytical sensitivity: 0.4 mg/dl.

3- **Total T3:**

The same as total T4 in the principle of the procedure, material supplied but here specific free T3 and quality control procedure. Expected value 81 - 179 ng/dl.

Analytical sensitivity 35 ng/dl.
4- FreeT3:

Principle of the procedure also competitive analogue-based immunoassay. The assay employs several features to preserve the equilibrium between free and protein-bound T3 and to measure accurately the unbound fraction. Incubation cycles $2 \times 30$ minutes.

Material supplied: free T3 test units: each code-labeled unit contains one bead coated with monoclonal murine anti-T3 antibody. Free T3 reagent wedges with brocades one of them (LF3A) contain 6.5 ml ligand-labeled T3 analog in buffer with preservative and (LF3B) and others 6.5 ml alkaline phosphatase conjugated to anti-ligand in buffer with preservative.

Expected values: 1.5 - 4.1 pg/ml.

Analytical sensitivity: 1.0 pg/ml

Quality control: also the same as mentioned above and the antibody is highly specific.

Linearity: since dilution shifts the equilibrium between free and protein-bound T3, so the assay can not be expected to maintain linearity under dilution.

**Interference and limitations:**

1- A variety of drugs which can affect the binding of T3 to the thyroid hormone carrier proteins.
2- Circulating autoantibody to T3 and hormone binding inhibitor.

3- Heparin has been reported to have both in vivo and in vitro effects on free thyroid hormones.

4- Heterophilic antibodies in human serum can react with immunoglobulins included with assay components. Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference.

5- In rare condition associated with extreme variations in albumin-binding capacity such as familial dysalbuminemia.

5- FreeT4:

*Principle of the procedure:* competitive immunoassay, incubation cycles. 2 x 30 minutes.

*Material supplied:* the same of free T3 but here specific for Free T4.

The Immulite free T4 procedure is a direct or single test assay, in the sense that its results are not calculated as a fraction of total T4, but interpolated from a stander curve calibrated in terms of free T4 concentration. In this aspect it differs from classic equilibrium dialysis methods and from so-called free T4 index determinations as well it requires neither a pre-incubation steps nor preliminary isolation of the free fraction by dialysis or column chromatography.
Quality control as mentioned above.

Expected values: euthyroid: 0.8 - 1.9 ng/dl.

Analytical sensitivity: 0.15 ng/dl.

Specificity: the antibody is highly specific for T4.

Interference the same as free T3.

**Statistical analysis:**

The data was entered into the computer. The statistical package (STATA) was used for analysis. The Chi-square test and t- student test were used to compare the data. A p value of less than 0.05 was considered statistically significant.

### 3. RESULTS

Sixty patients with acute and chronic non-thyroidal illness and 21 apparently healthy age and sex matched control subjects were studied using a chemiluminescent enzyme immunoassay of thyroid hormones. The results were compared with both reference values provided by the manufacturer of the assay kits and with the results of the control subjects.

#### 3.1. Characteristics of the studied patients:

#### 3.1.1. Age distribution:
Among the studied patients the ages ranged from 18-85 years. 21(35%) were between 41-60 years. 19 (31.67%) were aged between 21-40 years; 13 (21.67%) between 61-80 years; 5(8.33%) had ages less than or equal to 20 years and only 2(3.33%) were >80 years (Fig. 1).

3.1.2. Sex characteristics of the studied patients:

Fourty three patients (71.67%) were males and 17(28.33%) were females (Fig. 2)

3.1.3. Distribution of studied patients according to residence:

The majority, 50 (83.33%) of studied patients were from the middle of Sudan. Five (8.33%) were from the Eastern Sudan, two (3.33%) from the North, two (3.33%) were from the West and one (1.67%) was from the South (Fig. 3). MAP

3.2. Serum levels of thyroid hormones among ALL studied patients:

3.2.1. Thyroid stimulating hormone (TSH):

Fifty five (91.67%) of the studied patients had normal serum TSH (0.4 - 4 µ/u/ml), four (6.67%) had low serum TSH
(< 0.4 \mu/u/ml) and only one (1.66%) had high serum TSH (> 4 \mu/u/ml) (Fig. 4).

**3.2.2. Total thyroxin (TT4):**

Forty three (71.67%) of studied patients had normal TT4 (4.5 -12.5 \mu g/dl), 12(20%) had high TT4 and five (8.33%) had a low level of TT4 (Fig. 5).

**3.2.3. Total tri-iodothyronine (TT3):**

Thirty eight (63.33%) of the studied patients had low TT3 (<81 \mu g/dl), 22(36.67%) had normal TT3 (81-179 \mu g/dl), and none had high TT3 (Fig. 6). 20 patients out of the 38 with low TT3 had a TT3 level < 40 \mu g/dl.

**3.2.4. Free triiodothyronine level (FT3):**

Thirty-two (53.33%) of the studied patients had a low FT3 and 28 (46.67%) had normal FT3 (1.5 - 4.1 pg/ml) (Fig. 7).

**3.2.5. Free thyroxine level (FT4):**

Forty one (68.33%) of studied patients had normal FT4 (0.8 - 1.9 \mu g/dl) and 19 (31.67%) had low FT4 (Fig. 8).

**3.2.6. Distribution of studied patients according to the duration of illness:**

Thirty-eight (63.33%) patients had acute illness; 22 (36.67%) had chronic illness (Fig. 9).
3.2.7. Relation between TT3 and TT4 level in studied ALL patients:

Thirty-two (84.21%) of the studied patients with low TT3 had normal TT4; four (10.53%) had low TT4 and two (5.26%) had high TT4.

11 (50%) of the studied patients with normal TT3 had normal TT4, 10 (45.45%) had high TT4 and one (4.55%) had low TT4 (Table 1).

3.2.8. Relation between TT3 and TSH level in studied patients:

Thirty three (86.84%) of the patients with low T3 had normal TSH, 4 (10.53%) of patients with low TT3 had low TSH and 1(2.63%) patient had a high TSH. All patients with normal TT3 22(100%) had a normal TSH (Table 2).

3.2.9. Distribution of thyroid hormone profiles among studied patients:

Thirty two (53.33%) had low TT3 only with normal TT4 and TSH, 4 (6.67%) had low TT3, TT4 with normal TSH, one patient (1.67%) had low T3, TT4 and TSH, 12(20%) had high total T4 only 1 (18.33%) had a ‘normal’ thyroid profile (Table 3).

3.3 Alteration of thyroid hormone economy in relation to clinical condition of the patients:
All studied patients with low TSH (100%) were severely ill, the one patient who had high TSH was severely ill. (Table 4). TT4: four (80%) patients who had low TT4 were severely ill; 9 (75%) patients who had high TT4 were severely ill (Table 5). TT3: 28 (73.68) of studied patients with low TT3 were severely ill and 10) (26.31%) patients with low T3 were moderately ill (Table 6). FT3: 25 (78.13) patients with low free T3 were severely ill and 7 (21.87%) were moderately ill (Table 7). FT4: 14 (73.68) patients with low FT4 were severely ill and 5 (26.32) were moderately ill (Table 8).

3.4 Distribution of studied patients according to the duration of illness:

Thirty eight (63.33%) had acute illness, 22 (36.67%) had chronic illness (Fig. 9).

3.5. Alteration of thyroid hormone economy in relation to clinical diagnosis (Tables 9 -13):

3.5.1. Renal diseases:

Ten of studied patients had renal disease,( chronic renal failure and nephrotic syndrome)9 patients had normal TSH, one
patient had a high TSH, 8 patients had low T3 and 2 patients had low T4, while 7 patients had low free T3 and Free T4.

3.5.2. Tuberculosis:

six patients diagnosed with tuberculosis (pulmonary, abdominal, Pott’s disease), all patients had normal TSH and TT4, low TT3 and 5 had low FT3 and only one had low FT4.

3.5.3. Diabetes septic foot (DSF):

Three patients had DSF, all patients had normal TSH, TT4 and low TT3, two had low FT3 and one had low FT4.

3.5.4. Postoperative:

Six patients undergo major surgery, two of them had low TSH, 5 had low T3 and FT3 and only one had low T4 and 2 had low FT4.

3.5.5. Anaemic heart failure:

Two patients were suffering from anaemia; both of them had a normal thyroid profile.

3.5.6. Trauma:

Two patients had trauma (head and chest injury), both had normal TSH, one had low T3, FT3 and FT4 and another had high T4 with normal TT3, FT3 and FT4.

3.5.7. Infection:
Three patients diagnosed had infections, all of them had normal TSH, two had low TT3 and FT3, and one had low TT4 and FT4.

3.5.8. Central nervous system (CNS) disease:

Two patients had CNS disease; only one patient had a high TT4.

3.5.9. Diabetes:

One of studied patient diagnosed with DKA, had low TT3 and FT3.

3.5.10. Cardiovascular disease:

Seven patients suffering from heart failure, all of them had normal TSH, two of them had low TT3, FT3 and three had a high TT4 and one had low TT4.

Eight patients with ischemic heart disease (myocardial infarction and unstable angina admitted to CCU) all of them had normal TSH, FT3, FT4, only one had low T3 and 5 had high T4.

3.5.11. Liver diseases:

Four patients of studied patients diagnosed as portal hypertension, all of them had normal TSH, T4 and low T3. Three of them had low FT3 and FT4.
Five of the studied patients were diagnosed as hepatic failure. Two of them had low TSH, all of them had low T3, four had low FT3, three had low free T4 and only one had low T4.

3.6. Thyroid hormones profile in patients receiving drugs known to affect thyroid hormones levels:

Thirty eight (63.33%) of study population did not receive drugs that are known to affect thyroid hormone levels, 22(36.67) were receiving drugs that are known to affect thyroid hormone levels (Fig. 10).

TSH: all patients receiving medications known to affect thyroid hormone levels had TSH levels, which were statistically not different from those not receiving those medications (P = 0.206) (Table 14).

TT4: 9 patients were receiving medications known to affect thyroid hormones level had high TT4, which were statistically significant when compared to those not receiving those medications (P = 0.007) (Table 15).

TT3: 6 patients were receiving medications known to affect thyroid hormone levels had low TT3, which was statistically significant when compared to those not receiving those medications (P = 0.000) (Table 16).
FT4: 6 patients were receiving medications known to affect thyroid hormones levels and all had low FT4, which was statistically insignificant when compared to those not receiving those medications (P = 0.578) (Table 17).

FT3: 5 patients receiving medications known to affect thyroid hormones levels had low FT3, which was statistically significant when compared to those not receiving those medications (P = 0.000) (Table 18).

3.7. Control group:

3.7.1. Thyroid hormone levels in the control group:

Among studied controls TSH levels ranged between 0.46 - 2.3 µu/ml, total T4 level ranged between 5.02 - 11.5 µg/dl, total T3 level ranged between 80.1 - 140 ng/dl, free T3 ranged between 2.08 - 3.25pg/ml and free T4 ranged between 0.78 -1.2 ng/dl (Table 19).

3.7.2. Alteration in thyroid hormone levels in studied patients using the control group as a reference:

Table 20 shows alterations of TSH levels in the studied patients compared to the studied controls. The difference in results was statistically insignificant (P<t = 0.34.  P>t = 0.627)
Table 21 shows alterations of TT4 levels in the studied patients compared to the studied controls. The difference in results was statistically insignificant (P< t = 0.1477, P >t = 0.852).

Table 22 shows alteration of TT3 levels in the studied patients compared to the studied controls. The difference in results was statistically significant (P< t = 1.000; P >t = 0.000).

Table 23 shows alteration of FT3 levels in the studied patients compared to the studied controls. The difference in results was statistically significant (P< t = 0.999; P >t = 0.00000).

Table 24 shows alteration of FT4 levels in the studied patients compared to the studied controls. The difference in results was statistically insignificant (P< t = 0.8550; P >t = 0.145).
Figures
Table 1: Relation between TT3 and TT4 levels in studied patients

<table>
<thead>
<tr>
<th></th>
<th>TT4</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Relation between TT3 and TSH levels in studied patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4 (10.53%)</td>
<td>33 (86.84%)</td>
<td>1 (2.63%)</td>
<td>38 (100%)</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0%)</td>
<td>22 (100%)</td>
<td>0 (0.0%)</td>
<td>22 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>4 (6.67%)</td>
<td>55 (91.67%)</td>
<td>1 (1.66%)</td>
<td>60 (100%)</td>
</tr>
</tbody>
</table>

Table 3: Distribution of studied population according to thyroid hormone levels

<table>
<thead>
<tr>
<th>Thyroid hormones level</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low T3 only</td>
<td>32</td>
<td>53.33%</td>
</tr>
</tbody>
</table>
### Table 4: Alteration of TSH levels in studied population according to condition of the patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderately ill</td>
<td>Severely ill</td>
</tr>
<tr>
<td>Low</td>
<td>0 (0.0%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Normal</td>
<td>20 (36.36%)</td>
<td>35 (63.64%)</td>
</tr>
<tr>
<td>High</td>
<td>0 (0.0%)</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>

### Table 5: Alteration of TT4 levels in studied patients according to condition of the patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 6: Alteration of TT3 levels in studied patients according to condition of the patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>Moderately ill</th>
<th>Severely ill</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1 (20.0%)</td>
<td>4 (80%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Normal</td>
<td>16 (37.21%)</td>
<td>27 (62.79%)</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>High</td>
<td>03 (25.0%)</td>
<td>09 (75%)</td>
<td>12 (100%)</td>
</tr>
</tbody>
</table>

### Table 7: Alteration of FT3 levels in studied patients according to condition of the patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderately ill</td>
<td>Severely ill</td>
</tr>
<tr>
<td>Low</td>
<td>10 (26.32%)</td>
<td>28 (73.68%)</td>
</tr>
<tr>
<td>Normal</td>
<td>10 (45.46%)</td>
<td>12 (54.54%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Moderately ill</td>
<td>Severely ill</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Low</td>
<td>07 (21.87%)</td>
<td>25 (78.13%)</td>
</tr>
<tr>
<td>Normal</td>
<td>13 (46.43%)</td>
<td>15 (53.57%)</td>
</tr>
</tbody>
</table>

Table 8: Alteration of FT4 levels in studied patients according to condition of the patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Condition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderately ill</td>
<td>Severely ill</td>
</tr>
<tr>
<td>Low</td>
<td>05 (26.32%)</td>
<td>14 (73.68%)</td>
</tr>
<tr>
<td>Normal</td>
<td>15 (36.59%)</td>
<td>26 (63.41%)</td>
</tr>
</tbody>
</table>

Table 9: Alteration of TSH levels in studied patients according to the clinical diagnosis
<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Low</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Diabetic septic foot</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anaemic heart failure</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CNS disease</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular diseases (Heart failure)</td>
<td>0</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Cardiovascular disease (Ischemic heart disease)</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease (PHT)</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease (LF)</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4</td>
<td>55</td>
<td>1</td>
</tr>
</tbody>
</table>

P. = 0.561.

**Table 10: Alteration of TT3 levels in studied patients according to the clinical diagnosis**
<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Diabetic septic foot</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CNS disease</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
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<td></td>
</tr>
<tr>
<td>(Heart failure)</td>
<td>2</td>
<td>5</td>
<td>7</td>
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</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ischemic heart disease)</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Liver disease (PHT)</td>
<td>4</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Liver disease (LF)</td>
<td>5</td>
<td>0</td>
<td>5</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>38</td>
<td>22</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.000

Table 11: Alteration of TT4 levels in studied patients according to the clinical diagnosis
<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Low</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Diabetic septic foot</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Postoperative</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Anaemic heart failure</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CNS disease</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>(Heart failure)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>(Ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease (PHT)</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Liver disease (LF)</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
<td>43</td>
<td>12</td>
</tr>
</tbody>
</table>

P. = 0.362

Table 12: Alteration of FT3 levels in studied patients according to the clinical diagnosis
### Table 13: Alteration of FT4 levels in studied patients according to the clinical diagnosis

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Low</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Diabetic septic foot</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Postoperative</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Anaemic heart failure</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CNS disease</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>(Heart failure)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>(Ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease (PHT)</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Liver disease (LF)</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>28</td>
<td>60</td>
</tr>
</tbody>
</table>

P = 0.020
<table>
<thead>
<tr>
<th>Disease</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>7</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Diabetic septic foot</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Anaemic heart failure</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CNS disease</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Cardiovascular diseases</td>
<td>0</td>
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<td>7</td>
<td></td>
</tr>
<tr>
<td>(Heart failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>(Ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease (PHT)</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Liver disease (LF)</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>19</td>
<td>41</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

**P = 0.044**

Table 14: Effect of drugs on TSH levels in the studied patients
Table 15: Effect of drugs on T4 levels in the studied patients

<table>
<thead>
<tr>
<th>Drugs</th>
<th>T4 level</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not receiving drugs</td>
<td>Low</td>
<td>3</td>
<td>32</td>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>5</td>
<td>43</td>
<td>12</td>
<td>60</td>
</tr>
</tbody>
</table>

P = 0.007

Table 16: Effect of drugs on T3 levels in the studied patients

<table>
<thead>
<tr>
<th>Drugs</th>
<th>T3 level</th>
<th>Low</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.206
<table>
<thead>
<tr>
<th>Drugs</th>
<th>FT4 level</th>
<th>Low</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not receiving drugs</td>
<td></td>
<td>13</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>Receiving drugs</td>
<td></td>
<td>6</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>19</td>
<td>41</td>
<td>60</td>
</tr>
</tbody>
</table>

\( P = 0.578 \)

**Table 17: Effect of drugs on FT4 levels in the studied patients**

**Table 18: Effect of drugs on FT3 levels in the studied patients**
Table 19: Thyroid hormones level in the studied controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Observation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>21</td>
<td>0.46 μu/ml</td>
<td>2.3 μu/ml</td>
</tr>
<tr>
<td>TT4</td>
<td>21</td>
<td>5.02 μg/dl</td>
<td>11.5 μg/dl</td>
</tr>
<tr>
<td>TT3</td>
<td>21</td>
<td>80.1 ng/dl</td>
<td>140 ng/dl</td>
</tr>
<tr>
<td>FT3</td>
<td>11</td>
<td>2.08 pg/ml</td>
<td>3.25 pg/ml</td>
</tr>
<tr>
<td>FT4</td>
<td>11</td>
<td>0.78 ng/dl</td>
<td>1.2 ng/dl</td>
</tr>
</tbody>
</table>

P = 0.206

Table 20: Statistical test comparing TSH levels in the studied controls and patients
<table>
<thead>
<tr>
<th>Group</th>
<th>Observation</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>21</td>
<td>1.3052</td>
<td>0.4605</td>
</tr>
<tr>
<td>Patients</td>
<td>60</td>
<td>1.3967</td>
<td>0.9929</td>
</tr>
</tbody>
</table>

P < t = 0.3429  
P>t = 0.6571

Table 21: Statistical test comparing TT4 levels in the studied controls and patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>21</td>
<td>7.9314</td>
<td>1.9209</td>
</tr>
<tr>
<td>Patients</td>
<td>60</td>
<td>8.8265</td>
<td>3.7138</td>
</tr>
</tbody>
</table>

P < t = 0.1477  
P>t = 0.8523

Table 22: Statistical test comparing TT3 levels in the studied controls and patients
<table>
<thead>
<tr>
<th>Group</th>
<th>Observation</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>21</td>
<td>107.1667</td>
<td>18.10274</td>
</tr>
<tr>
<td>Patients</td>
<td>60</td>
<td>55.2533</td>
<td>44.83916</td>
</tr>
</tbody>
</table>

P < t = 1.0000  
P > t = 0.0000

**Table 23: Statistical test comparing FT3 levels in the studied controls and patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>2.5290</td>
<td>0.3636</td>
</tr>
<tr>
<td>Patients</td>
<td>60</td>
<td>1.21066</td>
<td>1.102485</td>
</tr>
</tbody>
</table>

P < t = 0.9999  
P > t = 0.0001

**Table 24: Statistical test comparing FT3 levels in the studied controls and patients**
4. DISCUSSION

For more than three decades it has been known that serum thyroid hormone levels drop during starvation and illnesses.\textsuperscript{65} To
characterized these changes and to correlate them with severity of the disease, types of illnesses and medications used during the illnesses, this study was done.

The majority of patients were above 40 years of age. Males predominated over females in this study because some of the female patients refused donation of a blood sample for research purposes.

Also patients from the central area of Sudan predominated, although they were from different tribes. This could be explained by migration of all these tribes to the central area in which this study was conducted. In this study these Sociodemographic characteristics may not be so important because people of all races and both sexes at any age are equally affected.\(^{63}\)

The non-thyroidal illnesses in this study were associated with a prompt decline in serum T3 and serum free T3 in about (63.33\%) and (53.33\%) of studied patients respectively. These results agree with the literature in that a reduction in TT3 was (40 - 100\%) of cases.\(^{63}\) Patients who had only TT3 reduction, a condition described as low T3 syndrome, occurred in 32 patients out of 38 with low TT3, The main explanation given for this syndrome is the reduction of T4 conversion to T3 by the hepatic deiodinase system, which is affected by cytokines,\(^{74,75,76}\) and selenium deficiency.\(^{79}\)
In the T3 syndrome rT3 is usually elevated, and it is important to differentiate the NTI syndrome from true hypothyroidism in which rT3 is also reduced. rT3 was not included in this study because no reagent for its assay was available in Sudan at the time of the study and also due to financial constraints on the research budget.

The thyroxine levels in the majority of studied patients were normal. 32 out of 43 with normal TT4 had low T3 and this supports what has been mentioned above in that a reduction of total T3 is due to a decrease of peripheral conversion of T4 to T3.

Five patients had low TT4, which usually occurs due to decreased T4 binding by TBG or existence of binding inhibitors. Another explanation is protease cleavage of TBG in inflammatory sites.\textsuperscript{(63)}

It has been reported that as the severity of illness progresses there is a gradual development of a more complex syndrome associated with both low T3 and low T4 levels.\textsuperscript{(63)} This occurred in 4 patients in this study who were severely ill and the total T3 was markedly low below the sensitivity of the instrument. They also had very low FT3 and FT4 and this agrees with the literature.\textsuperscript{(65)}

A number of studied patients had a high level of total T4 12 (20%). 10 of them had only high TT4. The majority of these 10
patients (8 patients) were suffering from cardiovascular problems and were admitted to the CCU.

In the literature many factors have been reported to increase total T4, but in this study drugs seemed to play a major role because most of the patients studied received amidarone hydrochloride (cardarone) and propranolol hydrochloride - drugs known to decrease thyroxine 5-deiodinase activity and so alter thyroxine to tri-iodothyronine metabolism. (63)

Two patients had a high TT4 but low TT3. No clear explanation was found for this finding but it has been suggested that such patients may have underlying subtle evidence of autonomous thyroid function that causes persistence of T4 secretion despite impairment of T4 metabolic clearance by illness in those patients and hence the TT3 level is reduced. (1)

Free T4 is believed to represent the hormone available to tissues and measurement of total serum T4 has only limited value. Nearly all of the circulating T4 is bound to TBG, TBP and albumin (ALB) (7,8)

41 of the studied patients (68.33%) had normal FT4 and we found that all patients with high TT4 had a normal FT4 and these findings support the explanation of high TT4 being due to the effect of medication and not true hyperthyroidism. 19 patients
(31.67%) had low FT4 and these patients were critically ill and suffering from renal and liver problems. This agrees with the literature that FT4 could be low, high or within the reference range. In this study no patient had a high level of FT4 because the results of FT4 assays in NTI are definitely method dependant and may be influenced by a variety of variables, including inhibitors present in serum, which may have been eliminated by the highly specific assay method used in this study. Also this study disagreed with a study reported in 1982 by Melmed, et al. In that study patients reported with non-thyroidal illness who had normal serum TT4 typically did not have reduced FT4 by most assay methods whereas in this study some patients had low FT4 in spite of normal TT4 and they were critically ill with very low levels of TT3 and FT3. The major problem in understanding the NTIs is in analyzing data on the level of FT4 because of the different assay methods used by different laboratories.

An important finding in this study is the normal TSH concentration in 55(91.67%) of patients which is highly suggestive of NTIS because TSH was not elevated in the presence of low T3 or T4 indicating that the patients are not hypothyroid. TSH was also not reduced in the presence of high TT4 indicating that the patients are not hyperthyroid and that these alterations are most probably
due to the effect of the illness which decreased the sensitivity of TSH secretion to serum T3 and T4 concentration.\(^{(65)}\)

Four patients who had a low level of TSH were severely ill and admitted to the ICU or comatose and they also had very low TT3 and FT3. This lowering of TSH is thought to be due to the effect of cytokines \(^{(80)}\) or drugs such as dopamine.\(^{(63)}\) The most important differential diagnosis here is secondary hypothyroidism in which also low TT3, TT4 and TSH test results occur and it is excluded by additional tests such as cortisol, gonadotropins and prolactin assays. One patient had elevated TSH. Elevation of TSH test results occurs commonly in patients recovering from illnesses.\(^{(63,65)}\)

In the euthyroid sick syndrome, the severity of illness has been correlated with the magnitude of changes observed,\(^{(89)}\) and it was clear in this study that alteration in thyroid function tests occurs more frequently in patients who are severely ill. In these patients illness may be complicated by number of medications.\(^{(1)}\) In such patients serum TT3 and FT3 were undetectable; serum T4 concentrations were reduced markedly or elevated. FT4 levels were abnormal and TSH was also low in these critically ill patients. The relation between reduction and severity of the disease was statistically significant in the case of FT3, because the more sick
the patient, the more metabolically adaptive he/she may be the lower the TT3 level.\(^{(89)}\) In this study some patients with cardiovascular disease who were severely ill had high TT4 with normal TT3. 75% of patients who had elevated TT4 level were severely ill. 91% of the patients had normal TSH, but all patients who had low TSH levels were severely ill.

Regarding the clinical diagnosis of studied patients, there are three major groups, renal, liver and cardiovascular disease. Patients suffering from renal problems, mainly chronic renal failure - most of them on regular dialysis, one of them diagnosed as nephrotic syndrome and his thyroid function test findings mimicked hypothyroidism, but basal TSH was unchanged and this agreed with the study by Ramirez, et al.\(^{(84)}\) Also in patients with chronic renal failure, there was significant reduction in the level of TT3, FT3 and FT4, but TSH was normal in all patients except one who had elevated TSH. This patient could be in the recovery phase which also agrees with the study by Ramirez, et al.\(^{(84)}\).

In patients suffering from cardiovascular disease - congestive heart failure or ischemic heart disease, the reduction of TT3 and FT3 was not like that in other severely ill patients and did not agree with the literature, because these patients, specially those who were admitted to the CCU (8 patients), had elevated TT4 which is
probably explained by the use of medications which also affect the metabolism of TT3, so TT3 was not markedly low or was even normal. The reduction of TT3 could be overcome by the effect of medication,\(^{(63)}\) especially in patients with myocardial infarction. The finding of normal TSH in all patients suggests that TSH may be important to differentiate between the euthyroid sick syndrome and hyper or hypothyroidism as the cause of cardiovascular disease especially congestive cardiac failure.

All patients suffering from liver problems had low TT3 and 7 out of 9 had low free T3 and this could be explained by the impairment of peripheral conversion of T4 to T3, which depends mainly on the liver. Only one patient had a low TT4. TSH level was reduced in 2 patients who had hepatic failure. This study partially agrees with the study done by Chopra, et al.\(^{(87)}\) This partial disagreement may have occurred because nearly half of these patients in this study were suffering from portal hypertension due to schistosomiasis. Such patients were not included in the study by Chopra, et al.\(^{(87)}\) Reduction of the hormones in patients with portal hypertension could be due to the effect of cytokines, nutritional status of the patient or any reason not published yet.

All patients suffering from tuberculosis had a marked reduction in TT3 level and low FT3, but normal TSH and TT4, so
the changes here are those of the T3 syndrome the causes of which have been mentioned previously.

The test results of thyroid function of patients studied postoperatively agrees with the literature (63) in that they had a reduction of TT3 and FT3. One patient had reduction in TT4 and 2 had a reduction of FT4 and TSH levels. These patients had major surgery and were admitted to the ICU and received many medications.

Regarding diabetes mellitus, 3 patients had diabetic septic foot and one had diabetic ketoacidosis. All of them showed reduction in TT3 and FT3 paralleling the decline in TT3. These patients had normal TSH and TT4 levels and this could be due to effect of the infection (63) or diabetes itself in which many metabolic disturbances occur.

Patients who presented with anaemic heart failure showed normal thyroid function. The cause of anaemia was not known yet and they were receiving blood transfusion which may have corrected the abnormality if it was present or that anaemia had no effect on thyroid function. This finding needs more study in a larger number of patients.

Patients suffering from infection showed some alteration in thyroid functions which agrees with the literature (63).
All patients mentioned above in this study showed a reduction of TT3, FT3 and FT4 (P = <0.05) and this agrees with other studies.(63,65)

It is clear that there was a statistically significant relation between drugs used and the alteration of thyroid function especially in TT4. This supports the explanation that elevated TT4 is due to the use of medications and is also supported by alteration in FT4 which was found to be statistically not significant.

TT3 and FT3 also showed significant reduction of their levels due to the effect of medication affecting thyroid function by many mechanisms. The most important is prevention of conversion of total T4 to T3 peripherally leading to reduction in total T3 because 80% of T3 is synthesized peripherally from T4 by the deiodinase system, causing a reduction in TT3 accompanied by a reduction in FT3.

Regarding the control group in this study we found that the maximum value of the hormone levels in this group was less than the upper limit of the reference range reported in the immulite® operator's manual. This could be due to the small sample size in this study compared with the numbers studied by the manufacturer to establish the reference range (usually 100 or more healthy individuals for different tests).
Another explanation could be that the range found in the control group is nearer to our actual reference range, so these limits should be considered as guidelines only. Each laboratory should establish its own reference range.

Comparing the test results of studied patients with studied controls, it was found that the reduction of TT3 and FT3 was statistically significant.

In this study most of the results agreed with studies conducted worldwide. However, there were some differences due to certain limitations. First, hormone assays are expensive in the Sudan, so only a small number of patients were investigated. This is not enough to characterize the pattern of the changes in each disease. Also rT3, an important test\(^{(63)}\) was not included in this study. Second, some patients in this study had no definitive diagnosis and their investigation was not complete. Third, some Sudanese patients (especially females) and their relatives refuse to donate blood samples. This resulted in a random selection of patients. Fourth, no established reference values for thyroid hormone levels in the Sudan exist. Fifth, no similar study was reported from the Sudan to consider it as a guideline. Finally, follow-up of referred patients is difficult in the Sudan.
There is currently a vast literature available on thyroid function test changes that occur during non-thyroidal illness. This wide topic needs more study to understand. Anyway, these results may add something to our knowledge about non-thyroidal illness in the Sudan.

CONCLUSION

This study concluded that reduction of T3 and free T3 were the most commonly encountered abnormalities in non-thyroidal illness (low T3 syndrome).
Several abnormal thyroid function patterns have been found in patients with serious non-thyroidal illness in this study, which could be categorized as follows:

1- Low T3 only.  
2- Low T3 and T4.  
3- Low T3, T4 and TSH.  
4- Elevated T4.

It has also been concluded that the degree of alteration in thyroid hormone levels appears to be correlated with the severity of non-thyroidal illness.

Abnormal thyroid hormone levels were more obvious in patients suffering from chronic renal failure, cardiovascular problems, liver disease, tuberculosis and post-major surgery.

Drugs that affect thyroid hormone levels had a significant effect in the test result abnormalities especially the level of T4. There was a difference between the maximum value of hormone levels in the study control group and that provided by the manual of the manufacturer of immulite ®.

RECOMMENDATIONS
Large, prospective, carefully controlled studies are needed for monitor thyroid function test findings during and after recovery from NTI.

Thyroid function tests should not be requested during illness unless there is strong clinical evidence of coexistence of thyroid disease, and should be repeated when non thyroidal illness resolves.

Informative, well-designed request forms are mandatory and also close rapport between the clinician and laboratory is important to facilitate good interpretation of test results.

Every laboratory should establish its own reference range and consider ranges provided by instrument or kit manufacturers as guidelines only.

Patients can be assured that this is a transient phenomenon and that normalization of thyroid function tests is expected with the patient’s recovery from non-thyroidal illness.

REFERENCES


76. Bartalena L, Brogionis, Grassol, et al. Relationship of the increased serum interleukin-6 concentration to changes of


Questionnaire

Euthyroid sick syndrome

• Serial No.: ........................................ Date.: ........................................

• Condition ........................................

1- Name: ..............................................................

2- Age (years): .................................

3- Sex: 1- Male ☐ 2 - Female ☐

4- Tribe: ........................................................................................................

5- Residence: .................................................................................................

6- Clinical diagnosis: ........................................................................................

7- Duration of illness (in months): .................................................................

8- History of thyroid illness or: .................................................................

   1- Surgery ☐ 2- Drug ☐ 3 -Radiiodine therapy ☐

9- Family history of thyroid disease: Yes ☐ No ☐

10- Drug used: ................................................................................................

11- Result of thyroid function test

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<th>TT4</th>
<th>TT3</th>
<th>FT4</th>
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Comment:
Appendix (2)
Equipment Data form

- **Name of equipment:** Imullite 1000.
- **Model:** Version 5.6.
- **Serial No.:** J. 3839 R.
- **Voltage:** 220 - 240.
- **Weight:** 80 kg.
- **Manufacture address:**
  - **Name:** DPC (Dignostic Products Corporation).
  - **Address:** Los Angeles- CA. 90045 USA,
    5700 West 96th street.
    Tel: (800) 372-1782.
    Fax: (800) 234 - 4372.